CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 91018

Name: Omega-3-Acid Ethyl Esters Capsules USP, 1 gram

Sponsor: Par Pharmaceutical, Inc.

Approval Date: June 24, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91018

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	**X**
Other Review(s)	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91018

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 091018

Par Pharmaceutical, Inc.
Attention: Janis A. Picurro
Director, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 10, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram.

Reference is also made to the Complete Response letter issued by this office on March 28, 2014, and to your amendments dated April 14, May 20, June 4, and June 5, 2014.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Omega-3-Acid Ethyl Esters Capsules USP, 1 gram, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Lovaza Capsules USP, 1 gram, of SmithKline Beecham (SKB). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, SKB's Lovaza Capsules, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,656,667 (the '667 patent), is scheduled to expire on April 10, 2017.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '667 patent is

invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Omega-3-Acid Ethyl Esters Capsules USP, 1 gram, under this ANDA. You have notified the agency that Par Pharmaceuticals (Par) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Par for infringement of the '667 patent within the statutory 45-day period in the United States District Court for the District of Delaware [Pronova BioPharma Norge AS v. Teva Pharmaceuticals USA, Inc., Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc., Civil Action No. 09-CV-0286]. You have also notified the agency that the United States Court of Appeals for the Federal Circuit found, in a mandate issued on September 12, 2013, that the asserted claims of the '667 patent are invalid.

With respect to 180-day generic drug exclusivity, we note that Par was a first applicant for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Par may be eligible for 180 days of generic drug exclusivity for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The agency notes that Par failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV)(forfeiture of exclusivity for failure to obtain tentative approval). The agency is not, however, making a formal determination at this time of Par's eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after a first applicant begins commercial marketing of Omega-3-Acid Ethyl Esters Capsules USP, 1 gram, or (b) at any time prior to the expiration of the listed patent if a first applicant has not begun commercial marketing. Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. You should advise the Office of Generic Drugs of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA)(Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as

described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

06/24/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91018

LABELING

NDC 49884-019-02

Omega-3-Acid Ethyl Esters Capsules USP

1 gram*

Pharmacist: Please dispense with patient package insert.

Swallow capsules whole

Rx only

60 Capsules

PAR PHARMACEUTICAL

***Each capsule contains:**
1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.

Each capsule provides:
Eicosapentaenoic acid (EPA) ethyl ester: 465 mg.
Docosahexaenoic acid (DHA) ethyl ester: 375 mg.

USUAL DOSAGE:
See package insert for full prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Protect from light.

Control No.:

Exp. Date:

I02/14

LA019-02-1-01

Manufactured for:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

Manufactured by:
Emcure Pharmaceuticals USA, Inc.
East Brunswick, NJ

F.P.O.

3 49884-019-02 0

NDC 49884-**019**-08

Omega-3-Acid Ethyl Esters Capsules USP

1 gram*

Pharmacist: Please dispense with patient package insert.

Swallow capsules whole

Rx only

120 Capsules

PAR PHARMACEUTICAL

***Each capsule contains:**
1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.

Each capsule provides:
Eicosapentaenoic acid (EPA) ethyl ester: 465 mg.
Docosahexaenoic acid (DHA) ethyl ester: 375 mg.

USUAL DOSAGE:
See package insert for full prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Protect from light.

Control No.:

Exp. Date:

I02/14

LA019-08-1-01

Manufactured for:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

Manufactured by:
Emcure Pharmaceuticals USA, Inc.
East Brunswick, NJ

F.P.O.

N 49884-019-082

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Omega-3-acid ethyl esters safely and effectively. See full prescribing information for Omega-3-acid ethyl esters capsules.

Omega-3-Acid Ethyl Esters Capsules USP, for oral use

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Indications and Usage, Limitations of Use **(1)** 06/2013

INDICATIONS AND USAGE

Omega-3-acid ethyl esters is a combination of ethyl esters of omega 3 fatty acids, principally EPA and DHA, indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia (HTG). **(1)**

Limitations of Use:

- The effect of omega-3-acid ethyl esters on the risk for pancreatitis has not been determined. **(1)**
- The effect of omega-3-acid ethyl esters on cardiovascular mortality and morbidity has not been determined. **(1)**

DOSAGE AND ADMINISTRATION

- The daily dose of omega-3-acid ethyl esters is 4 grams per day taken as a single 4-gram dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily). **(2)**
- Patients should be advised to swallow omega-3-acid ethyl esters capsules whole. Do not break open, crush, dissolve or chew omega-3-acid ethyl esters. **(2)**

DOSAGE FORMS AND STRENGTHS

Capsules: 1-gram **(3)**

CONTRAINDICATIONS

Omega-3-acid ethyl esters is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to omega-3-acid ethyl esters or any of its components. **(4)**

WARNINGS AND PRECAUTIONS

- In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. **(5.1)**
- Omega-3-acid ethyl esters may increase levels of LDL. Monitor LDL levels periodically during therapy. **(5.1)**
- Use with caution in patients with known hypersensitivity to fish and /or shellfish. **(5.2)**
- There is a possible association between omega-3-acid ethyl esters and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first months of initiating therapy. **(5.3)**

ADVERSE REACTIONS

The most common adverse reactions (incidence >3% and greater than placebo) were eructation, dyspepsia and taste perversion. **(6)**

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Omega-3-acids may prolong bleeding time. Patients taking omega-3-acid ethyl esters and an anticoagulant or other drug affecting coagulation (e.g., anti-platelet agents) should be monitored periodically. **(7.1)**

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. **(8.1)**

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Issued: 05/2014

0100T9-02

OMEGA-3-ACID ETHYL ESTERS CAPSULES USP

R 05/14

010019-02

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Omega-3-acid ethyl esters is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia (HTG).

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet before receiving omega-3-acid ethyl esters and should continue this diet during treatment with omega-3-acid ethyl esters.

Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting therapy with omega-3-acid ethyl esters. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Limitations of Use:

The effect of omega-3-acid ethyl esters on the risk for pancreatitis has not been determined.

The effect of omega-3-acid ethyl esters on cardiovascular mortality and morbidity has not been determined.

2 DOSAGE AND ADMINISTRATION

- Assess triglyceride levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate. *[see* **Indications and Usage (1)***]*.
- Patients should be placed on an appropriate lipid-lowering diet before receiving omega-3-acid ethyl esters, and should continue this diet during treatment with omega-3-acid ethyl esters. In clinical studies, omega-3-acid ethyl esters was administered with meals.

The daily dose of Omega-3-Acid Ethyl Esters Capsules, USP is 4 grams per day. The daily dose may be taken as a single 4-gram dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily).

Patients should be advised to swallow omega-3-acid ethyl esters capsules whole. Do not break open, crush, dissolve or chew omega-3-acid ethyl esters.

3 DOSAGE FORMS AND STRENGTHS

Omega-3-acid ethyl esters capsules are supplied as 1-gram transparent soft-gelatin capsules filled with clear to yellowish liquid and bearing the designation P019.

4 CONTRAINDICATIONS

Omega-3-acid ethyl esters is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to omega-3-acid ethyl esters or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring: Laboratory Tests

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with omega-3-acid ethyl esters. In some patients, increases in ALT levels without a concurrent increase in AST levels were observed.

In some patients, omega-3-acid ethyl esters increases LDL-C levels. LDL-C levels should be monitored periodically during therapy with omega-3-acid ethyl esters.

Laboratory studies should be performed periodically to measure the patient's TG levels during therapy with omega-3-acid ethyl esters.

5.2 Fish Allergy

Omega-3-acid ethyl esters contains ethyl esters of omega-3 fatty acids (EPA and DHA) obtained from the oil of several fish sources. It is not known whether patients with allergies to fish and/or shellfish, are at increased risk of an allergic reaction to omega-3-acid ethyl esters. Omega-3-acid ethyl esters should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

5.3 Recurrent Atrial Fibrillation (AF) or Flutter

In a double-blind, placebo-controlled trial of 663 subjects with symptomatic paroxysmal AF (n=542) or persistent AF (n=121), recurrent AF or flutter was observed in subjects randomized to omega-3-acid ethyl esters who received 8 grams/day for 7 days and 4 grams/day thereafter for 23 weeks at a higher rate relative to placebo. Subjects in this trial had median baseline triglycerides of 127 mg/dL, had no substantial structural heart disease, were taking no anti-arrhythmic therapy (rate control permitted), and were in normal sinus rhythm at baseline.

At 24 weeks, in the paroxysmal AF stratum, there were 129 (47%) first recurrent symptomatic AF or flutter events on placebo and 141 (53%) on omega-3-acid ethyl esters [primary endpoint, HR 1.19; 95% CI: 0.93, 1.35]. In the persistent AF stratum, there were 19 (35%) events on placebo and 34 (52%) events on omega-3-acid ethyl esters [HR 1.63; 95% CI: 0.91, 2.18]. For both strata combined, the HR was 1.25; 95% CI: 1.00, 1.40. Although the clinical significance of these results is uncertain, there is a possible association between omega-3-acid ethyl esters and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first 2 to 3 months of initiating therapy.

Omega-3-acid ethyl esters is not indicated for the treatment of AF or flutter.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions reported in at least 3% and at a greater rate than placebo for subjects treated with omega-3-acid ethyl esters based on pooled data across 23 clinical studies are listed in **Table 1**.

Table 1. Adverse Reactions Occurring at Incidence ≥3% and Greater than Placebo in Clinical Trials of omega-3-acid ethyl esters

	Omega 3 (N = 655)		Placebo (N = 370)	
Adverse Reaction[a]	**n**	**%**	**n**	**%**
Eructation	29	4	5	1
Dyspepsia	22	3	6	2
Taste perversion	27	4	1	<1

[a] Trials included subjects with HTG and severe HTG.

Additional adverse reactions from clinical studies are listed below:

Digestive System: Constipation, gastrointestinal disorder and vomiting.

Metabolic and Nutritional Disorders: Increased ALT, and increased AST.

Skin: Pruritus, and rash.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the events described below have been identified during post-approval use of omega-3-acid ethyl esters. Because these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

The following events have been reported: anaphylactic reaction, hemorrhagic diathesis

7 DRUG INTERACTIONS

7.1 Anticoagulants or Other Drugs Affecting Coagulation

Some trials with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these trials has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical trials have not been done to thoroughly examine the effect of omega-3-acid ethyl esters and concomitant anticoagulants. Patients receiving treatment with omega-3-acid ethyl esters and an anticoagulant or other drug affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether omega-3-acid ethyl esters can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Omega-3-acid ethyl esters should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Animal Data:

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 grams/day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day beginning 2 weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 grams/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1,000, 3,000, and 6,000 mg/kg/day from gestation day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In pregnant rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2,000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3,000 mg/kg/day (7 times the human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 375, 750, and 1,500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion on the infant of a nursing mother is unknown; caution should be exercised when omega-3-acid ethyl esters is administered to a nursing mother. An animal study in lactating rats given oral gavage ^{14}C-ethyl EPA demonstrated that drug levels were 6 to 14 times higher in milk than in plasma.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

A limited number of subjects older than 65 years were enrolled in the clinical trials of omega-3-acid ethyl esters. Safety and efficacy findings in subjects older than 60 years did not appear to differ from those of subjects younger than 60 years.

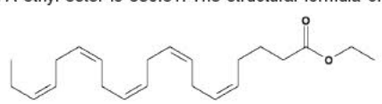
9 DRUG ABUSE AND DEPENDENCE

Omega-3-acid ethyl esters does not have any known drug abuse or withdrawal effects.

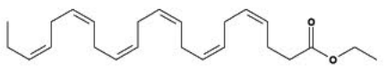
11 DESCRIPTION

Omega-3-acid ethyl esters, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each 1-gram capsule of omega-3-acid ethyl esters contains at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oils. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).

The structural formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51. The structural formula of EPA ethyl ester is:



The structural formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55. The structural formula of DHA ethyl ester is:



Omega-3-Acid Ethyl Esters Capsules USP, also contain the following inactive ingredients: gelatin, glycerol, and purified water, α-tocopherol, 3.8-4.2 mg/capsule, (components of the capsule shell), shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxide, n-butyl alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of omega-3-acid ethyl esters is not completely understood. Potential mechanisms of action include inhibition of acyl-CoA: 1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Omega-3-acid ethyl esters may reduce the synthesis of triglycerides in the liver because EPA and DHA are

◄ PHARMACIST - DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

Omega-3-Acid Ethyl Esters Capsules USP

Read this Patient Information before you start taking omega-3-acid ethyl esters, and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is Omega-3-Acid Ethyl Esters Capsules?

Omega-3-acid ethyl esters is a prescription medicine, used along with a low fat and low cholesterol diet to lower very high triglyceride (fat) levels in adults.

It is not known if omega-3-acid ethyl esters changes your risk of having inflammation of your pancreas (pancreatitis).

It is not known if omega-3-acid ethyl esters prevents you from having a heart attack or stroke.

It is not known if omega-3-acid ethyl esters is safe and effective in children.

Who should not take Omega-3-Acid Ethyl Esters Capsules?

Do not take omega-3-acid ethyl esters if you are allergic to omega-3-acid ethyl esters or any of the ingredients in omega-3-acid ethyl esters. See the end of this leaflet for a complete list of ingredients in omega-3-acid ethyl esters.

What should I tell my doctor before taking Omega-3-Acid Ethyl Esters Capsules?

Before you take Omega-3-acid ethyl esters, tell your doctor if you:

- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- have a certain heart rhythm problem called atrial fibrillation or flutter.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to omega-3-acid ethyl esters.
- are pregnant, or plan to become pregnant. It is not known if omega-3-acid ethyl esters will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Omega-3-acid ethyl esters can pass into your breast milk. You and your doctor should decide if you will take omega-3-acid ethyl esters or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicine, vitamins, and herbal supplements.

Omega-3-acid ethyl esters can interact with certain other medicines that you are taking. Using omega-3-acid ethyl esters with medicines that affect blood clotting (anticoagulants or blood thinners) may cause serious side effects.

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist when you get a new medicine.

How should I take Omega-3-Acid Ethyl Esters Capsules?

- Take omega-3-acid ethyl esters exactly as your doctor tells you to take it.
- You should not take more than 4 capsules of omega-3-acid ethyl esters each day. Either take all 4 capsules at one time, or 2 capsules two times a day.
- Do not change your dose or stop omega-3-acid ethyl esters without talking to your doctor..
- Take omega-3-acid ethyl esters with or without food.
- Take omega-3-acid ethyl esters capsules whole. Do not break, crush, dissolve, or chew omega-3-acid ethyl esters capsules before swallowing. If you cannot swallow omega-3-acid ethyl esters capsules whole, tell your doctor. You may need a different medicine.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol and carbohydrates, and low in added sugars before giving you omega-3-acid ethyl esters. Stay on this diet while taking omega-3-acid ethyl esters.
- Your doctor should do blood tests to check your triglyceride, bad cholesterol and liver function levels while you take omega-3-acid ethyl esters.

(continued) ►

What are the possible side effects of Omega-3-Acid Ethyl Esters Capsules?

Omega-3-acid ethyl esters may cause serious side effects, including:

- increases in the results of blood tests used to check your liver function (ALT and AST) and your bad cholesterol levels (LDL-C).
- increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking omega-3-acid ethyl esters if you already have that problem.

The most common side effects of omega-3-acid ethyl esters include:

- burping
- upset stomach
- a change in your sense of taste

Talk to your doctor if you have a side effect that bothers you or does not go away.

These are not all the possible side effects of omega-3-acid ethyl esters. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Omega-3-Acid Ethyl Esters Capsules?

- Store omega-3-acid ethyl esters at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from light.
- Do not freeze omega-3-acid ethyl esters.
- Safely throw away medicine that is out of date or no longer needed.

Keep omega-3-acid ethyl esters and all medicines out of the reach of children.

General information about the safe and effective use of omega-3-acid ethyl esters: Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use omega-3-acid ethyl esters for a condition for which it was not prescribed. Do not give omega-3-acid ethyl esters to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information Leaflet summarizes the most important information about omega-3-acid ethyl esters. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about omega-3-acid ethyl esters that is written for health professionals

For more information call Par Pharmaceutical at 1-800-828-9393.

What are the ingredients in Omega-3-Acid Ethyl Esters Capsules?

Active Ingredient: omega-3-acid ethyl esters, mostly EPA and DHA

Inactive Ingredients: gelatin, glycerol, and purified water, α-tocopherol, 3.8-4.2 mg/capsule (components of the capsule shell), shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxide, n-butyl alcohol.

This patient labeling has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Par Pharmaceutical Companies, Inc.
Spring Valley, New York 10977

Manufactured by:
Emcure Pharmaceuticals USA, Inc.
East Brunswick, NJ

Revised: 05/14 PI019-01-1-02

poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

12.3 Pharmacokinetics

In healthy volunteers and in subjects with hypertriglyceridemia, EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (omega-3-acid ethyl esters) induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters.

Specific Populations:

Age: Uptake of EPA and DHA into serum phospholipids in subjects treated with omega-3-acid ethyl esters was independent of age (<49 years versus ≥49 years).

Gender: Females tended to have more uptake of EPA into serum phospholipids than males. The clinical significance of this is unknown.

Pediatric: Pharmacokinetics of omega-3-acid ethyl esters have not been studied.

Renal or Hepatic Impairment: Omega-3-acid ethyl esters have not been studied in patients with renal or hepatic impairment.

Drug-Drug Interactions:

Simvastatin:
In a 14-day trial of 24 healthy adult subjects, daily coadministration of simvastatin 80 mg with omega-3-acid ethyl esters 4 grams did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.

Atorvastatin:
In a 14-day trial of 50 healthy adult subjects, daily coadministration of atorvastatin 80 mg with omega-3-acid ethyl esters 4 grams did not affect AUC or C_{max} of exposure to atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin at steady state.

Rosuvastatin:
In a 14-day trial of 48 healthy adult subjects, daily coadministration of rosuvastatin 40 mg with omega-3-acid ethyl esters 4 grams did not affect AUC or C_{max} of exposure to rosuvastatin at steady state.

In vitro studies using human liver microsomes indicated that clinically significant cytochrome P450 mediated inhibition by EPA/DHA combinations are not expected in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a rat carcinogenicity study with oral gavage doses of 100, 600, and 2,000 mg/kg/day, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 grams/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, and 2,000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation, and lactation. No adverse effect on fertility was observed at 2,000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 Severe Hypertriglyceridemia

The effects of omega-3-acid ethyl esters 4 grams per day were assessed in 2 randomized, placebo-controlled, double-blind, parallel-group trials of 84 adult subjects (42 on omega-3-acid ethyl esters, 42 on placebo) with very high triglyceride levels. Subjects whose baseline triglyceride levels were between 500 and 2,000 mg/dL were enrolled in these 2 trials of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these subjects were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.

The changes in the major lipoprotein lipid parameters for the groups receiving omega-3-acid ethyl esters or placebo are shown in **Table 2**.

Table 2. Median Baseline and Percent Change From Baseline in Lipid Parameters in Subjects with Severe Hypertriglyceridemia (≥500 mg/dL)

Parameter	omega-3-acid ethyl esters N = 42		Placebo N = 42		Difference
	BL	% Change	BL	% Change	
TG	816	-44.9	788	+6.7	-51.6
Non-HDL-C	271	-13.8	292	-3.6	-10.2
TC	296	-9.7	314	-1.7	-8.0
VLDL-C	175	-41.7	175	-0.9	-40.8
HDL-C	22	+9.1	24	0.0	+9.1
LDL-C	89	+44.5	108	-4.8	+49.3

BL = Baseline (mg/dL); % Change = Median Percent Change from Baseline; Difference = omega-3-acid ethyl esters Median % Change – Placebo Median % Change

Omega-3-acid ethyl esters 4 grams per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Treatment with omega-3-acid ethyl esters to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.

The effect of omega-3-acid ethyl esters on the risk of pancreatitis has not been determined.

The effect of omega-3-acid ethyl esters on cardiovascular mortality and morbidity has not been determined.

16 HOW SUPPLIED/STORAGE AND HANDLING

Omega-3-Acid Ethyl Esters Capsules USP are supplied as 1-gram oblong shaped soft gelatin capsules filled with clear to yellowish liquid and bearing the designation P019.

NDC 49884-019-02 Bottles of 60
NDC 49884-019-08 Bottles of 120

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Protect from light.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Information for Patients

- Omega-3-acid ethyl esters should be used with caution in patients with known sensitivity or allergy to fish and/or shellfish *[see* **Warnings and Precautions (5.2)***]*.
- Advise patients that use of lipid-regulating agents does not reduce the importance of adhering to diet *[see* **DOSAGE AND ADMINISTRATION (2)***]*.
- Advise patients not to alter omega-3-acid ethyl esters capsules in any way and to ingest intact capsules only *[see* **DOSAGE AND ADMINISTRATION (2)***]*.
- Instruct patients to take omega-3-acid ethyl esters as prescribed. If a dose is missed, advise patients to take it as soon as they remember. However, if they miss one day of omega-3-acid ethyl esters, they should not double the dose when they take it.

PATIENT INFORMATION
Omega-3-Acid Ethyl Esters Capsules USP

Read this Patient Information before you start taking omega-3-acid ethyl esters, and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is Omega-3-Acid Ethyl Esters Capsules?

Omega-3-acid ethyl esters is a prescription medicine, used along with a low fat and low cholesterol diet to lower very high triglyceride (fat) levels in adults.

It is not known if omega-3-acid ethyl esters changes your risk of having inflammation of your pancreas (pancreatitis).

It is not known if omega-3-acid ethyl esters prevents you from having a heart attack or stroke.

It is not known if omega-3-acid ethyl esters is safe and effective in children.

Who should not take Omega-3-Acid Ethyl Esters Capsules?

Do not take omega-3-acid ethyl esters if you are allergic to omega-3-acid ethyl esters or any of the ingredients in omega-3-acid ethyl esters. See the end of this leaflet for a complete list of ingredients in omega-3-acid ethyl esters.

What should I tell my doctor before taking Omega-3-Acid Ethyl Esters Capsules?

Before you take Omega-3-acid ethyl esters, tell your doctor if you:

- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- have a certain heart rhythm problem called atrial fibrillation or flutter.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to omega-3-acid ethyl esters.
- are pregnant, or plan to become pregnant. It is not known if omega-3-acid ethyl esters will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Omega-3-acid ethyl esters can pass into your breast milk. You and your doctor should decide if you will take omega-3-acid ethyl esters or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicine, vitamins and herbal supplements.

Omega-3-acid ethyl esters can interact with certain other medicines that you are taking. Using omega-3-acid ethyl esters with medicines that affect blood clotting (anticoagulants or blood thinners) may cause serious side effects.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Omega-3-Acid Ethyl Esters Capsules?

- Take omega-3-acid ethyl esters exactly as your doctor tells you to take it.
- You should not take more than 4 capsules of omega-3-acid ethyl esters each day. Either take all 4 capsules at one time, or 2 capsules two times a day.
- Do not change your dose or stop omega-3-acid ethyl esters without talking to your doctor.
- Take omega-3-acid ethyl esters with or without food.
- Take omega-3-acid ethyl esters capsules whole. Do not break, crush, dissolve, or chew omega-3-acid ethyl esters capsules before swallowing. If you cannot swallow omega-3-acid ethyl esters capsules whole, tell your doctor. You may need a different medicine.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol and carbohydrates, and low in added sugars before giving you omega-3-acid ethyl esters. Stay on this diet while taking omega-3-acid ethyl esters.
- Your doctor should do blood tests to check your triglyceride, bad cholesterol and liver function levels while you take omega-3-acid ethyl esters.

What are the possible side effects of Omega-3-Acid Ethyl Esters Capsules?

Omega-3-acid ethyl esters may cause serious side effects, including:

- increases in the results of blood tests used to check your liver function (ALT and AST) and your bad cholesterol levels (LDL-C).
- increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking omega-3-acid ethyl esters if you already have that problem.

The most common side effects of omega-3-acid ethyl esters include:

- burping
- upset stomach
- a change in your sense of taste

Talk to your doctor if you have a side effect that bothers you or does not go away.

These are not all the possible side effects of omega-3-acid ethyl esters. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Omega-3-Acid Ethyl Esters Capsules?

- Store omega-3-acid ethyl esters at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from light.
- Do not freeze omega-3-acid ethyl esters.
- Safely throw away medicine that is out of date or no longer needed.

Keep omega-3-acid ethyl esters and all medicines out of the reach of children.

General information about the safe and effective use of omega-3-acid ethyl esters: Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use omega-3-acid ethyl esters for a condition for which it was not prescribed. Do not give omega-3-acid ethyl esters to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information Leaflet summarizes the most important information about omega-3-acid ethyl esters. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about omega-3-acid ethyl esters that is written for health professionals.

For more information call Par Pharmaceutical at 1-800-828-9393

What are the ingredients in Omega-3-Acid Ethyl Esters Capsules?

Active Ingredient: omega-3-acid ethyl esters, mostly EPA and DHA

Inactive Ingredients: gelatin, glycerol, and purified water, α-tocopherol, 3.8-4.2 mg/capsule (components of the capsule shell), shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxide, n-butyl alcohol.

This patient labeling has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Par Pharmaceutical Companies, Inc.
Spring Valley, New York 10977

Manufactured by:
Emcure Pharmaceuticals USA, Inc.
East Brunswick, NJ

Revised: 05/14 OS019-01-1-02

PATIENT INFORMATION

Omega-3-Acid Ethyl Esters Capsules USP

Read this Patient Information before you start taking omega-3-acid ethyl esters, and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is Omega-3-Acid Ethyl Esters Capsules?
Omega-3-acid ethyl esters is a prescription medicine, used along with a low fat and low cholesterol diet to lower very high triglyceride (fat) levels in adults.

It is not known if omega-3-acid ethyl esters changes your risk of having inflammation of your pancreas (pancreatitis).

It is not known if omega-3-acid ethyl esters prevents you from having a heart attack or stroke.

It is not known if omega-3-acid ethyl esters is safe and effective in children.

Who should not take Omega-3-Acid Ethyl Esters Capsules?
Do not take omega-3-acid ethyl esters if you are allergic to omega-3-acid ethyl esters or any of the ingredients in omega-3-acid ethyl esters. See the end of this leaflet for a complete list of ingredients in omega-3-acid ethyl esters.

What should I tell my doctor before taking Omega-3-Acid Ethyl Esters Capsules?
Before you take Omega-3-Acid Ethyl Esters Capsules, tell your doctor if you:
- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- have a certain heart rhythm problem called atrial fibrillation or flutter.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to omega-3-acid ethyl esters.
- are pregnant, or plan to become pregnant. It is not known if omega-3-acid ethyl esters will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Omega-3-acid ethyl esters can pass into your breast milk. You and your doctor should decide if you will take omega-3-acid ethyl esters or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicine, vitamins, and herbal supplements.

Omega-3-acid ethyl esters can interact with certain other medicines that you are taking. Using omega-3-acid ethyl esters with medicines that affect blood clotting (anticoagulants or blood thinners) may cause serious side effects.

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist when you get a new medicine.

How should I take Omega-3-Acid Ethyl Esters Capsules?
- Take omega-3-acid ethyl esters exactly as your doctor tells you to take it.
- You should not take more than 4 capsules of omega-3-acid ethyl esters each day. Either take all 4 capsules at one time, or 2 capsules two times a day.
- Do not change your dose or stop omega-3-acid ethyl esters without talking to your doctor.
- Take omega-3-acid ethyl esters with or without food.
- Take omega-3-acid ethyl esters capsules whole. Do not break, crush, dissolve, or chew omega-3-acid ethyl esters capsules before swallowing. If you cannot swallow omega-3-acid ethyl esters capsules whole, tell your doctor. You may need a different medicine.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol and carbohydrates, and low in added sugars before giving you omega-3-acid ethyl esters. Stay on this diet while taking omega-3-acid ethyl esters.
- Your doctor should do blood tests to check your triglyceride, bad cholesterol and liver function levels while you take omega-3-acid ethyl esters.

What are the possible side effects of Omega-3-Acid Ethyl Esters Capsules?
Omega-3-acid ethyl esters may cause serious side effects, including:
- increases in the results of blood tests used to check your liver function (ALT and AST) and your bad cholesterol levels (LDL-C).
- increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking omega-3-acid ethyl esters if you already have that problem.

The most common side effects of omega-3-acid ethyl esters include:
- burping
- upset stomach
- a change in your sense of taste

Talk to your doctor if you have a side effect that bothers you or does not go away.

These are not all the possible side effects of omega-3-acid ethyl esters. For more information, ask your doctor or pharmacist.

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How should I store Omega-3-Acid Ethyl Esters Capsules?
- Store omega-3-acid ethyl esters at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from light.
- Do not freeze omega-3-acid ethyl esters.
- Safely throw away medicine that is out of date or

no longer needed.

Keep Omega-3-Acid Ethyl Esters Capsules and all medicines out of the reach of children.

General information about the safe and effective use of Omega-3-Acid Ethyl Esters Capsules: Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use omega-3-acid ethyl esters for a condition for which it was not prescribed. Do not give omega-3-acid ethyl esters to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information Leaflet summarizes the most important information about omega-3-acid ethyl esters. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about omega-3-acid ethyl esters that is written for health professionals

For more information call Par Pharmaceutical at 1-800-828-9393.

What are the ingredients in Omega-3-Acid Ethyl Esters Capsules?

Active Ingredient: omega-3-acid ethyl esters, mostly EPA and DHA

Inactive Ingredients: gelatin, glycerol, and purified water, α-tocopherol, 3.8-4.2 mg/capsule (components of the capsule shell), shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxide, n-butyl alcohol.

This patient labeling has been approved by the U.S. Food and Drug Administration.

Manufactured for:
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Spring Valley, New York 10977

Manufactured by:
Emcure Pharmaceuticals USA, Inc.
East Brunswick, NJ

Issued: 04/14 PD019-01-1-01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91018

LABELING REVIEWS

****This AP summary supersedes the AP Summary review dated 4/24/2014, in DARRTS****

APPROVAL SUMMARY

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (6th Cycle)

ANDA Number:	091018
Date of Submission:	May 20, 2014 June 4, 2014 (no labeling pieces to review)
Applicant:	Par Pharmaceutical, Inc.
Established Name and Strength:	Omega-3-Acid Ethyl Esters Capsules USP, 1 gram
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☐ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☒ No Comments **(**Labeling Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated May 20, 2014.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL? No

After the ANDA is approved, the reviewer for the first labeling supplement may consider asking the firm for the following revisions and revised labels and labeling may be submitted in the next annual report:

1. CONTAINER: We encourage you to add a comma (,) between the established name and

USP.

2. **INSERT:** HIGHLIGHTS, Title- Revise the established name to read "OMEGA-3-ACID ETHYL ESTERS capsules USP, for oral use".
3. **PATIENT PACKAGE INSERT**: We encourage you to include the phonetic spelling of the established name directly below the title.
4. **SPL**: We note in the SPL data elements, your capsule size is 4mm. Please confirm. Please also provide a comparison of your capsule size with the reference listed drug.

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER Bottles of 60s Bottles of 120s	4/14/2014	Final	Acceptable for approval
INSERT	5/20/2014	Final	Acceptable for approval
PATIENT INFORMATION attached to Insert labeling	5/20/2014	Final	Acceptable for approval
STAND ALONE PATIENT INFORMATION	4/14/2014		
SPL	5/20/2014		None

FOR THE RECORD: Please note the first 2 review cycles were completed by labeling reviewer Thuyanh Vu.

1. **MODEL LABELING:** This review is based on the labeling for Lovaza® (omega-3-acid ethyl esters) Capsules of SmithKline Beecham, (NDA 021654/S-041) approved May 14, 2014.

   S-041 provides for a revised package insert to remove "14.2 Other Clinical Experience" to comply with 21 CFR 201.57(c) (15)(i).

   The labeling approved on 9/11/2013 does not usually require new labeling. This labeling was approved for manufacturing change or addition. Supplement -039 was submitted to add Catalent (b) (4) as an alternate drug product manufacturing site, and associated labeling revisions. The initial submission did not contain labeling, so this was submitted in an amendment to the application.

   The labeling approved 6/26/2013 (s-037) provides for revised package insert in response to the letter dated 12/18/2012.

   <u>BACKGROUND INFORMATION FROM RPM LABELING REVIEW dated 6/30/2013:</u>
   Lovaza was approved 11/10/2004 for the treatment of severe hypertriglyceridemia. Vascepa (icosapent ethyl) Capsules (NDA 202057) was approved 7/26/2012 for the same indication. These are the only 2 currently approved fish oil prescription products available. Following the approval of Vascepa, there were some inconsistencies noted between the package inserts of Vascepa and Lovaza, and a supplement request letter was issued to the

sponsor of Lovaza on 12/18/2012, requesting some labeling revisions (letter attached). The firm responded with this labeling supplement.

Editorial revisions were made to the labeling as well as the following sections were revised for consistency between the two labeling.

PI

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion on the infant of a nursing mother is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. An animal study in lactating rats given oral gavage 14C-ethyl EPA demonstrated that drug levels were 6 to 14 times higher in milk than in plasma.

PPI

"What should I tell my doctor before taking LOVAZA?

Before you take LOVAZA, tell your doctor if you:

….are breastfeeding or plan to breastfeed. LOVAZA can pass into your breast milk. You and your doctor should decide if you will take LOVAZA or breastfeed."

Container (from Supp-039 approved 9/11/2013) in DARRTS

MedWatch – (checked June 3, 2014)

No new reports since new labeling approved May 14, 2014.

The information below is located in the last approved labeling for the RLD.

Lovaza (omega-3-acid ethyl esters) capsules

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research

(CDER)

September 2012

5 WARNINGS AND PRECAUTIONS

5.3 Recurrent Atrial Fibrillation (AF) or Flutter

- In a double-blind, placebo-controlled trial of 663 patients with symptomatic paroxysmal AF (n=542) or persistent AF (n=121), recurrent AF or flutter was observed in patients randomized to LOVAZA who received 8 grams/day for 7 days and 4 grams/day thereafter for 23 weeks at a higher rate relative to placebo. .....

- .....Although the clinical significance of these results is uncertain, there is a possible association between LOVAZA and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first 2 to 3 months of initiating therapy. LOVAZA is not indicated for the treatment of AF or flutter.

Patient Information Leaflet

What are the possible side effects of LOVAZA?

LOVAZA may cause serious side effects, including:

increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking LOVAZA if you already have that problem.

2. **USP-37:** (checked June 3, 2014)

This product is the subject of a USP monograph.

Omega-3-Acid Ethyl Esters Capsules

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature. Do not freeze. Protect from light.

• **Labeling:** The label states the amount of docosahexaenoic acid (DHA) ethyl ester and eicosapentaenoic acid (EPA) ethyl ester, and the minimum amount of total content of omega-3-acid ethyl esters in mg/Capsule. It also states the name and content of any added antioxidant.

3. **PATENT AND EXCLUSIVITY**

Patent Data – NDA 021654

No	Expiration	Use Code	Use	How filed	Labeling Impact
5656667	Apr 10, 2017	U-822	Use in Lipid Management	PIV	None

Exclusivity Data– There is no unexpired exclusivity for this product.

PATENT AMENDMENT DATED 3/18/2012

The following information was taken from the cover letter dated 3/18/2012

Based on discussions between Par and the Office of Generic Drugs ("OGD"), we understand that the administrative record for the ANDA is complete, and that there are no outstanding requests for additional data or information from OGD. The only substantive impediment to approval of the application appears to be OGD's ongoing consideration of the criteria under which it may approve a generic version of the RLD, given its composition and derivation (components obtained from the body oil of certain species of fish). There is ample administrative precedent supporting the approval of generic products referencing naturally-derived drugs that were approved through the new drug approval process, and we urge OGD to rely on this precedent in bringing its review of the ANDA to a prompt resolution. In fact, Par has a compelling need to obtain final approval of its ANDA in the very near future, as the court handling the associated paragraph IV litigation recently announced that a decision in that litigation will issue shortly. In order to position Par to market its generic product promptly upon successful resolution of the litigation – a result we expect – we respectfully request a meeting with OGD as soon as possible to identify and resolve any remaining issues associated with the approvability of the ANDA, with the goal of facilitating timely approval of the application.

We also note that Par is vested with a right to 180-day marketing exclusivity upon approval of its ANDA, notwithstanding OGD's three-year review of the application. In particular, the forfeiture provisions set forth in the federal Food, Drug and Cosmetic Act ("FDCA") indicate that there should be no forfeiture of exclusivity for the ANDA, as FDA's protracted deliberation appears to be due to the Agency's ongoing review of the requirements for approval of generic versions of the RLD.[1] Accordingly, we seek to confirm FDA's understanding that Par's hard-won right to 180-day exclusivity has not been, and will not be, forfeited as a result of OGD's drawn out review of the ANDA.

PATENT AMENDMENT DATED MARCH 24, 2011

Please be advised that an action for alleged infringement of the '077 and '667 patents was brought in the U.S. District Court for the District of Delaware ("the Delaware litigation") before the expiration of the 45 day period as described in Section 505(j)(5)(B)(iii) of the FFDCA. Please also be advised that, as a result of Par's August 05, 2010 notice, the allegations in the Delaware litigation were amended to include alleged infringement of the '488 patent.

Par certifies that sale of drug product will not begin until after expiry of the above exclusivities.

In patent amendment dated 5/1/09- Par was sued on the infringement of patents '077 and '594 in the District Court of District of Delaware.

4. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:
gelatin, glycerol, and purified water, α-tocopherol, 3.8-4.2 mg/capsule, (components of the capsule shell), shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxide, n-butyl alcohol.

5. **MANUFACTURING FACILITY**

Emcure Pharmaceuticals USA, Inc.
21b Cotters Lane
East Brunswick, NJ 08816

6. **FINISHED PRODUCT DESCRIPTION**

RLD: 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

ANDA: 1 –gram oblong shaped soft gelatin capsule filled with clear to yellowish liquid and bearing the designation "P019".

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Do not freeze. KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

8. **PRODUCT LINE**

RLD: 1 gram capsules in bottles of 120s

ANDA: The drug product will be packaged in 60s and 120s

9. **CONTAINER/CLOSURE [2.3.P.7-original submission]**

Container Closure Systems for Omega-3-Acid Ethyl Esters Capsules		
Strength	Presentation	Description of Container/Closure System
1 g	Standard Retail Bottle 60 count	(b) (4)
	Standard Retail Bottle 120 count	(b) (4)
		(b) (4)

10. **PATIENT PACKAGE INSERT**

The firm provided the stand-alone PPI in amendment dated 4/14/2014.

11. **BIOEQUIVALENCE/DISSOLUTION:** Bio dissolution review, overall dissolution review results are adequate as of review dated 3/25/2014.

12. **RELATED APPLICATIONS: None**

13. **AMENDMENT SUBMITTED 6/4/2014:** There were no labeling pieces to review. A separate labeling amendment was previously submitted on 5/20/2014.

14. **SPL DATA ELEMENTS: submitted 2/29/2014 section 1.14.1.3**

ANDA:

900 mg: Size = 4 mm

RLD:

900 mg: Size = 24 mm

Email sent to CMC Reviewer regarding Capsule Size

From:
Sent: Friday, April 25, 2014 8:22 AM

To:
Subject: RE: ANDA 091018 Omega-3-Acid Ethyl Esters Capsule by Par

Thanks for your queries. I don't know where you find the softgel cap size at 4mm manufactured by Par. Per the following spec for encapsulation mentioned in the executed batch record, the size would be (b) (4) mm (b) (4) die size).

List of Equipment

From:
Sent: Thursday, April 24, 2014 9:47 AM
To:
Subject: ANDA 091018 Omega-3-Acid Ethyl Esters Capsule by Par

The RLD list the size of their capsule as 24 mm. In the SPL DATA Elements, Par listed the size of their capsule as 4 mm. Can you confirm the size of the capsule for Par?

15. EXPRESSION OF STRENGTH:

There is a Citizen Petition memorandum available under the RLD regarding the expression of strength dated January 23, 2014.

The Office of Regulatory Policy (ORP) has requested a consult on the citizen petition submitted by John H. Fuson, Crowell & Moring, LLP, on February 6, 2013 (Petition FDA-2013-P-0148): However, given the prior practice for other naturally-sourced mixtures, it is not unreasonable to maintain the status quo of designating the entire fish oil mixture as the active ingredient with a strength of 1 g, as was concluded by the Center Director in the November 18, 2013 Center Director Decisional Briefing.

Agency letter dated 6/18/12 for NDA 021654:
According to Lovaza's approved specification, each capsule contains from 950 mg to 1050 mg of esterified purified fish oil. The principal components are two omega-3-acid ethyl esters, eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester. Both are required to be present at a combined concentration of between 800 and 880 mg/capsule. The drug substance specification also includes an acceptance criterion of at least 90% (w/w) total omega-3-ethyl esters – the active ingredients.

Recently reviewed data from your NDA indicate that the total omega-3-ethyl esters content does not deviate significantly from 90% of total capsule fill. For the target 1 gram capsule fill, this amounts to 900 mg of omega-3 ethyl esters. Consequently, we believe that the labeled strength should be changed from 1 gram to 900 mg.

Please revise all labeling to reflect a strength per capsule of 900 mg.

NDA sponsor response dated 8/6/2012:

GSK is not in agreement that the labeled strength of LOVAZA should be changed to 900 mg (see **Attachment 1** for details).

GSK proposes to revise the Dosage Forms and Strengths section of the Prescribing Information to incorporate the language that is currently used on the trade and sample container packaging:
• Each capsule contains 1 gram omega-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.
This change to the Prescribing Information would afford a consistent description of the product (in the PI and on the container labels) and would alleviate any potential misunderstandings regarding the amount of active ingredient in a 1 gram capsule. Division consideration and concurrence with this proposal would be much appreciated.

The attachment provided by the firm in the 8/6/2012 amendment provides a detailed explanation of the inactive ingredients.

Email from TL's regarding expression of strength dated 5/7/2013

From:
Sent: Tuesday, May 07, 2013 3:29 PM
To:
Subject: FW: Strength on PDP (Omega-3)

From:
Sent: Tuesday, May 07, 2013 2:36 PM
To:
Subject: RE: Strength on PDP (Omega-3)

I agree. What if the RLD gets approved with a different strength?

From:
Sent: Tuesday, May 07, 2013 2:09 PM
To:
Cc:
Subject: RE: Strength on PDP (Omega-3)

I believe the strength should appear on the PDP as we do with all our products. All vitamins that I buy do have the strength. Might even be better to express as mg rather than grams. There are many others on google image.

<< File: images[2].jpg >> << File: images[1].jpg >> << File: images[3].jpg >>

From:
Sent: Tuesday, May 07, 2013 1:18 PM
To:
Subject: Strength on PDP (Omega-3)

What do you think about the following situation….

RLD Label: (strength not specified on the PDP)

<< File: image[10].jpg >>

OSE review dated 4/27/2004 for the RLD

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

The request for the strength on the PDP seemed to have stopped there.

What are your thoughts….should we be the same as the RLD and remain silent on the strength or ask the firm to include the strength "1 gram*" on the PDP pursuant to the Guidance for Industry?

The **principal display panel** (PDP) is the panel of a label that is most likely to be displayed, presented, shown, or examined by the end user. We recommend that the PDP include the following critical information:

- ☐ Proprietary name
- ☐ **Established name** or **proper name**
- ☐ Product strength
- ☐ Route(s) of administration

☐ Warnings (if any) or cautionary statements (if any)

What are your thoughts?

From:
Sent: Tuesday, May 07, 2013 1:02 PM
To:
Subject: RE: ANDA (b) (4)

I like having the strength on the PDP, but would we be following the RLD or is that difference allowed? I do not have a problem with asking the firm to include the strength on the PDP. Do you know of other cases like this?

(b) (4)

If we put the 1 gm on the PDP, I think we will need the asterisk because it consists of at least 900 mg Omega-3-acid ethyl esters.

No rush. Any time is fine with me.

Thanks,

From:
Sent: Tuesday, May 07, 2013 12:41 PM
To:
Subject: RE: ANDA (b) (4)

OSE review dated 4/27/2004

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

However, I can't find the amendment where the firm responded to this request.

Personally, I do not see a reason why we shouldn't include the strength. Maybe we can do a "Upon further consideration, we encourage you to include the expression of strength on the principal display panel."

Do you think we need an asterisk after "1 gram*" and before the "Each capsule contains" statement?

What do you think?

P.S. I just started my review so probably won't send it back to you until tomorrow.

Date of Review:	June 3, 2014
Primary Reviewer:	Betty Turner
Acting Team Leader:	Theresa Liu

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BETTY B TURNER
06/05/2014

THERESA C LIU
06/05/2014
Acting for Ruby Wu

APPROVAL SUMMARY

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (5th Cycle)

ANDA Number:	091018
Date of Submission:	April 14, 2014
Applicant:	Par Pharmaceutical, Inc.
Established Name and Strength:	Omega-3-Acid Ethyl Esters Capsules USP, 1 gram
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☐ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☒ No Comments **(**Labeling Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated April 14, 2014.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL? No.

After the ANDA is approved, the reviewer for the first labeling supplement may consider asking the firm for the following revisions and revised labels and labeling may be submitted in the next annual report:

1. **CONTAINER:** We encourage you to add a comma (,) between the established name and USP.
2. **INSERT:** HIGHLIGHTS, Title- In the established name, revise “Capsule” to read “capsule” (use lower case “c”).

3. **PATIENT PACKAGE INSERT**: We encourage you to include the phonetic spelling of the established name directly below the title.
4. **SPL**: We note in the SPL data elements, your capsule size is 4mm. Please confirm. Please also provide a comparison of your capsule size with the reference listed drug.

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER Bottles of 60s	4/14/2014	Final	Acceptable for approval
Bottles of 120s	4/14/2014		
INSERT	4/14/2014	Final	Acceptable for approval
PATIENT INFORMATION	4/14/2014	Final	Acceptable for approval
SPL	2/19/2014		None

FOR THE RECORD: Please note that the first 2 review cycles were completed by labeling reviewer Thuyanh Vu.

1. **MODEL LABELING**: This review is based on the labeling for Lovaza® (omega-3-acid ethyl esters) Capsule of SmithKline Beecham, (NDA 021654/S-039) approved September 11, 2013.

   The labeling approved on 9/11/2013 does not usually require new labeling. This labeling was approved for manufacturing change or addition. Supplement -039 was submitted to add Catalent (b) (4) as an alternate drug product manufacturing site, and associated labeling revisions. The initial submission did not contain labeling, so this was submitted in an amendment to the application.

   The labeling approved 6/26/2013 (s-037) provides for revised package insert in response to the letter dated 12/18/2012.

   BACKGROUND INFORMATION FROM RPM LABELING REVIEW dated 6/30/2013:

   Lovaza was approved 11/10/2004 for the treatment of severe hypertriglyceridemia.

   Vascepa (icosapent ethyl) Capsules (NDA 202057) was approved 7/26/2012 for the same indication. These are the only 2 currently approved fish oil prescription products available. Following the approval of Vascepa, there were some inconsistencies noted between the package inserts of Vascepa and Lovaza, and a supplement request letter was issued to the sponsor of Lovaza on 12/18/2012, requesting some labeling revisions (letter attached). The firm responded with this labeling supplement.

   Editorial revisions were made to the labeling as well as the following sections were revised for consistency between the two labeling.

   PI

   8.3 Nursing Mothers

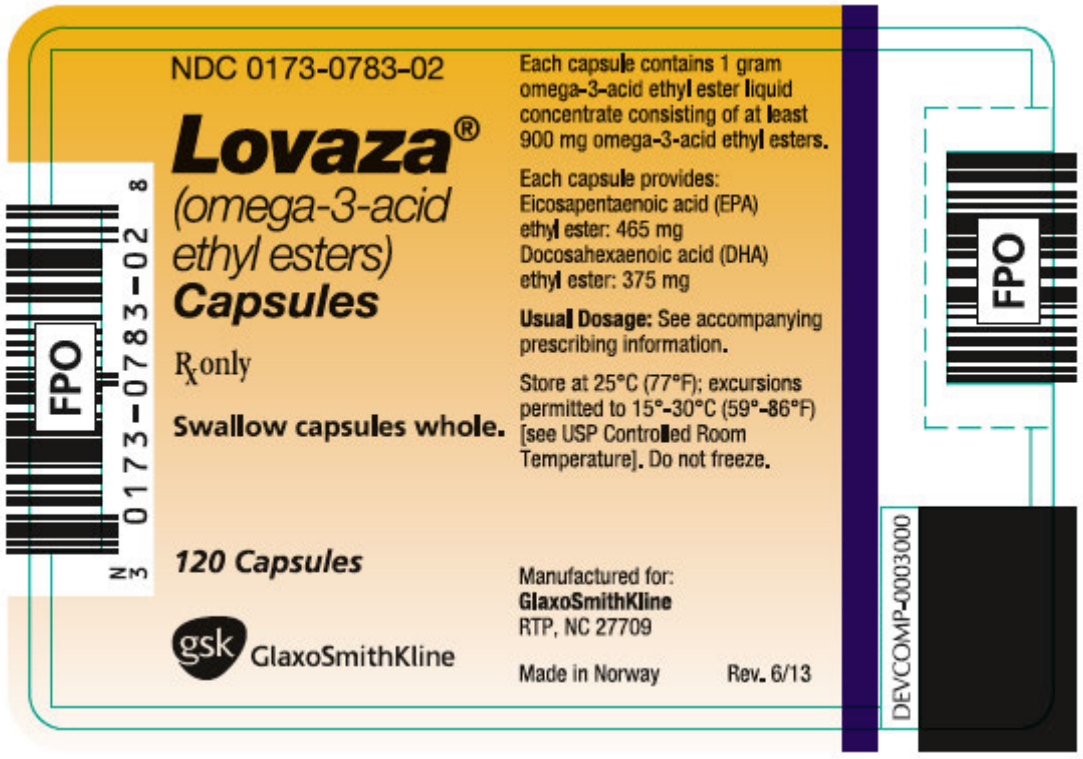
   Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion on the infant of a nursing mother is unknown; caution should be

exercised when VASCEPA is administered to a nursing mother. An animal study in lactating rats given oral gavage 14C-ethyl EPA demonstrated that drug levels were 6 to 14 times higher in milk than in plasma.

PPI

"What should I tell my doctor before taking LOVAZA?
Before you take LOVAZA, tell your doctor if you:
….are breastfeeding or plan to breastfeed. LOVAZA can pass into your breast milk. You and your doctor should decide if you will take LOVAZA or breastfeed."

Container (from Supp-039 approved 9/11/2013) in DARRTS



MedWatch – (checked April 21, 2014)

No new reports since new labeling approved September 2012

The information below is located in the last approved labeling for the RLD.

Lovaza (omega-3-acid ethyl esters) capsules

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)

September 2012

5 WARNINGS AND PRECAUTIONS

5.3 Recurrent Atrial Fibrillation (AF) or Flutter

- In a double-blind, placebo-controlled trial of 663 patients with symptomatic paroxysmal AF (n=542) or persistent AF (n=121), recurrent AF or flutter was observed in patients randomized to LOVAZA who

received 8 grams/day for 7 days and 4 grams/day thereafter for 23 weeks at a higher rate relative to placebo. .....

- .....Although the clinical significance of these results is uncertain, there is a possible association between LOVAZA and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first 2 to 3 months of initiating therapy. LOVAZA is not indicated for the treatment of AF or flutter.

Patient Information Leaflet

What are the possible side effects of LOVAZA?

LOVAZA may cause serious side effects, including:

increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking LOVAZA if you already have that problem.

2. **USP-36:** (checked April 21, 2014)

This product is the subject of a USP monograph.

Omega-3-Acid Ethyl Esters Capsules

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature. Do not freeze. Protect from light.

• **Labeling:** The label states the amount of docosahexaenoic acid (DHA) ethyl ester and eicosapentaenoic acid (EPA) ethyl ester, and the minimum amount of total content of omega-3-acid ethyl esters in mg/Capsule. It also states the name and content of any added antioxidant.

3. **PATENT AND EXCLUSIVITY**

Patent Data – NDA 021654

No	Expiration	Use Code	Use	How filed	Labeling Impact
5656667	Apr 10, 2017	U-822	Use in Lipid Management	PIV	None

Exclusivity Data– There is no unexpired exclusivity for this product.

PATENT AMENDMENT DATED 3/18/2012

The following information was taken from the cover letter dated 3/18/2012

Based on discussions between Par and the Office of Generic Drugs ("OGD"), we understand that the administrative record for the ANDA is complete, and that there are no outstanding requests for additional data or information from OGD. The only substantive impediment to approval of the application appears to be OGD's ongoing consideration of the criteria under which it may approve a generic version of the RLD, given its composition and derivation (components obtained from the body oil of certain species of fish). There is ample administrative precedent supporting the approval of generic products referencing naturally-derived drugs that were approved through the new drug approval process, and we urge OGD to rely on this precedent in bringing its review of the ANDA to a prompt resolution. In fact, Par has a compelling need to obtain final approval of its ANDA in the very near future, as the court handling the associated paragraph IV litigation recently announced that a decision in that litigation will issue shortly. In order to position Par to market its generic product promptly upon successful resolution of the litigation – a result we expect – we respectfully request a meeting with OGD as soon as possible to identify and resolve any remaining issues associated with the approvability of the ANDA, with the goal of facilitating timely approval of the application.

We also note that Par is vested with a right to 180-day marketing exclusivity upon approval of its ANDA, notwithstanding OGD's three-year review of the application. In particular, the forfeiture provisions set forth in the federal Food, Drug and Cosmetic Act ("FDCA") indicate that there should be no forfeiture of exclusivity for the ANDA, as FDA's protracted deliberation appears to be due to the Agency's ongoing review of the requirements for approval of generic versions of the RLD.[1] Accordingly, we seek to confirm FDA's understanding that Par's hard-won right to 180-day exclusivity has not been, and will not be, forfeited as a result of OGD's drawn out review of the ANDA.

PATENT AMENDMENT DATED MARCH 24, 2011

Please be advised that an action for alleged infringement of the '077 and '667 patents was brought in the U.S. District Court for the District of Delaware ("the Delaware litigation") before the expiration of the 45 day period as described in Section 505(j)(5)(B)(iii) of the FFDCA. Please also be advised that, as a result of Par's August 05, 2010 notice, the allegations in the Delaware litigation were amended to include alleged infringement of the '488 patent.

Par certifies that sale of drug product will not begin until after expiry of the above exclusivities.

In patent amendment dated 5/1/09- Par was sued on the infringement of patents '077 and '594 in the District Court of District of Delaware.

4. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:
gelatin, glycerol, and purified water, α-tocopherol, 3.8-4.2 mg/capsule, (components of the capsule shell), shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxide, n-butyl alcohol.

5. **MANUFACTURING FACILITY**

Emcure Pharmaceuticals USA, Inc.
21b Cotters Lane
East Brunswick, NJ 08816

6. **FINISHED PRODUCT DESCRIPTION**

RLD: 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

ANDA: 1 –gram oblong shaped soft gelatin capsule filled with clear to yellowish liquid and bearing the designation "P019".

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Do not freeze. KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN

8. **PRODUCT LINE**

RLD: 1 gram capsules in bottles of 120s

ANDA: The drug product will be packaged in 60s and 120s

9. **CONTAINER/CLOSURE[2.3.P.7-original submission]**

Container Closure Systems for Omega-3-Acid Ethyl Esters Capsules		
Strength	Presentation	Description of Container/Closure System
1 g	Standard Retail Bottle 60 count	(b) (4)
	Standard Retail Bottle 120 count	(b) (4)
		(b) (4)

10. **PATIENT PACKAGE INSERT**

The firm provided the stand-alone PPI in amendment dated 4/14/2014.

11. **BIOEQUIVALENCE/DISSOLUTION:** Bio dissolution review, overall dissolution review results are adequate as of review dated 3/25/2014.

12. **RELATED APPLICATIONS: None**

13. **SPL DATA ELEMENTS: submitted 2/19/14 section 1.14.1.3**

ANDA:

900 mg: Size = 4 mm

RLD:

900 mg: Size = 24 mm

Email sent to CMC Reviewer 4/24/2014

From:
Sent:Thursday, April 24, 2014 9:47 AM
To:
Subject:ANDA 091018 Omega-3-Acid Ethyl Esters Capsule by Par

The RLD list the size of their capsule as 24 mm. In the SPL DATA Elements, Par listed the size of their capsule as 4 mm. Can you confirm the size of the capsule for Par?

14. **EXPRESSION OF STRENGTH:**

There is a Citizen Petition memorandum available under the RLD regarding the expression of strength dated January 23, 2014.

The Office of Regulatory Policy (ORP) has requested a consult on the citizen petition submitted by John H. Fuson, Crowell & Moring, LLP, on February 6, 2013 (Petition FDA-2013-P-0148): However, given the prior practice for other naturally-sourced mixtures, it is not unreasonable to maintain the status quo of designating the entire fish oil mixture as the active ingredient with a strength of 1 g, as was concluded by the Center Director in the November 18, 2013 Center Director Decisional Briefing.

Agency letter dated 6/18/12 for NDA 021654:
According to Lovaza's approved specification, each capsule contains from 950 mg to 1050 mg of esterified purified fish oil. The principal components are two omega-3-acid ethyl esters, eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester. Both are required to be present at a combined concentration of between 800 and 880 mg/capsule. The drug substance specification also includes an acceptance criterion of at least 90% (w/w) total omega-3-ethyl esters – the active ingredients.

Recently reviewed data from your NDA indicate that the total omega-3-ethyl esters content does not deviate significantly from 90% of total capsule fill. For the target 1 gram capsule fill, this amounts to 900 mg of omega-3 ethyl esters. Consequently, we believe that the labeled strength should be changed from 1 gram to 900 mg.

Please revise all labeling to reflect a strength per capsule of 900 mg.

NDA sponsor response dated 8/6/2012:
GSK is not in agreement that the labeled strength of LOVAZA should be changed to 900 mg (see **Attachment 1** for details).

GSK proposes to revise the Dosage Forms and Strengths section of the Prescribing Information to incorporate the language that is currently used on the trade and sample container packaging:
• Each capsule contains 1 gram omega-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.
This change to the Prescribing Information would afford a consistent description of the product (in the PI and on the container labels) and would alleviate any potential misunderstandings regarding the amount of active ingredient in a 1 gram capsule. Division consideration and concurrence with this proposal would be much appreciated.

The attachment provided by the firm in the 8/6/2012 amendment provides a detailed explanation of the inactive ingredients.

Email from TL's regarding expression of strength dated 5/7/2013

From:
Sent: Tuesday, May 07, 2013 3:29 PM
To:
Subject: FW: Strength on PDP (Omega-3)

From:
Sent: Tuesday, May 07, 2013 2:36 PM
To:
Subject: RE: Strength on PDP (Omega-3)

I agree. What if the RLD gets approved with a different strength?

From:
Sent: Tuesday, May 07, 2013 2:09 PM
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Subject: RE: Strength on PDP (Omega-3)

I believe the strength should appear on the PDP as we do with all our products. All vitamins that I buy do have the strength. Might even be better to express as mg rather than grams. There are many others on google image.

<< File: images[2].jpg >> << File: images[1].jpg >> << File: images[3].jpg >>

From:
Sent: Tuesday, May 07, 2013 1:18 PM
To:
Subject: Strength on PDP (Omega-3)

What do you think about the following situation….

RLD Label: (strength not specified on the PDP)

<< File: image[10].jpg >>

OSE review dated 4/27/2004 for the RLD

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

The request for the strength on the PDP seemed to have stopped there.

What are your thoughts….should we be the same as the RLD and remain silent on the strength or ask the firm to include the strength "1 gram*" on the PDP pursuant to the Guidance for Industry?

The **principal display panel** (PDP) is the panel of a label that is most likely to be displayed, presented, shown, or examined by the end user. We recommend that the PDP include the following critical information:

- ☐ Proprietary name
- ☐ **Established name** or **proper name**
- ☐ Product strength
- ☐ Route(s) of administration
- ☐ Warnings (if any) or cautionary statements (if any)

What are your thoughts?

From:
Sent: Tuesday, May 07, 2013 1:02 PM
To:
Subject: RE: ANDA (b) (4)

I like having the strength on the PDP, but would we be following the RLD or is that difference allowed? I do not have a problem with asking the firm to include the strength on the PDP. Do you know of other cases like this?

(b) (4)

If we put the 1 gm on the PDP, I think we will need the asterisk because it consists of at least 900 mg Omega-3-acid ethyl esters.

No rush. Any time is fine with me.

Thanks,

From:
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To:
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OSE review dated 4/27/2004

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

However, I can't find the amendment where the firm responded to this request.

Personally, I do not see a reason why we shouldn't include the strength. Maybe we can do a "Upon further consideration, we encourage you to include the expression of strength on the principal display panel."

Do you think we need an asterisk after "1 gram*" and before the "Each capsule contains" statement?

What do you think?

P.S. I just started my review so probably won't send it back to you until tomorrow.

Date of Review: April 21, 2014

Primary Reviewer:	Betty Turner
Acting Team Leader:	Angela Payne

Following this page, 6 Pages of Draft Labeling have been Withheld in Full as (b)(4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BETTY B TURNER
04/24/2014

ANGELA M PAYNE
04/24/2014
ATL

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (4th cycle)

ANDA Number:	091018
Date of Submission:	February 19, 2014
Applicant:	Par Pharmaceutical, Inc.
Established Name and Strength:	Omega-3-Acid Ethyl Esters Capsules USP, 1 gram
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☒ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☐ No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on February 27, 2014, based on your submission dated February 19, 2014.

1. CONTAINER (120s)

   The container labels submitted on February 19, 2014 are blurry and difficult to read. Please revise and submit labels in final print in a text based PDF file instead of image based.

2. INSERT

   a. HIGHLIGHTS, Title: We encourage you to use upper case letter for the drug substance and lower case letter for the dosage form and route of administration.

   b. Revise "Omega-3" to read Omega-3-Acid ethyl esters" [2 occurrences (Heading in Table 1 and Table 2)].

   c. Inactive Ingredients: You listed the content of α-tocopherol to be 3.8 to 4.2 mg/capsule in the amendment dated 2/19/2014. However, in your response to the labeling deficiency dated 11/18/2009, you stated the following.

   Labeling comment:
   GENERAL COMMENT:
   We note that you do not have "α-tocopherol" listed as an inactive ingredient. However, in 2.3.P.5(original submission), the content of α-tocopherol is stated as (b) (4) *mg/capsule. Please explain this discrepancy.*

   Firm's Response
   The content of "α-tocopherol" was inadvertently omitted from the listing of inactive

ingredients in the insert. The content of α-tocopherol as [redacted] *mg/capsule is now listed as an inactive ingredient in the insert*

Please explain this discrepancy.

3. PATIENT INFORMATION LEAFLET
   a. Please include the dosage form in the established name when reference is made to the drug product.
   b. Refer to INSERT comment 2(c).

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL?

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER Bottles of 60s and 120s	2/19/2014	Final- 60s Draft- 120s	Revisions requested for 120s
INSERT	2/19/2014	Final	Revisions requested
PATIENT INFORMATION	2/19/2014	Final	Revisions requested

REMS required? NO. **(OTC do NOT require)**

MedGuides and/or PPIs (505-1(e))	☐ Yes	☐ No
Communication plan (505-1(e))	☐ Yes	☐ No

Revised October 2013

Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☐ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☐ No
Timetable for assessment (505-1(d))	☐ Yes	☐ No

FOR THE RECORD: Please note the first 2 review cycles were completed by labeling reviewer Thuyanh Vu.

1. **MODEL LABELING**: This review is based on the labeling for Lovaza® (omega-3-acid ethyl esters) Capsule of SmithKline Beecham, (NDA 021654/S-039) approved September 11, 2013.

   The labeling approved on 9/11/2013 does not usually require new labeling. This labeling was approved for manufacturing change or addition. Supplement -039 was submitted to add Catalent (b) (4) as an alternate drug product manufacturing site, and associated labeling revisions. The initial submission did not contain labeling, so this was submitted in an amendment to the application.

   The labeling approved 6/26/2013 (s-037) provides for revised package insert in response to the letter dated 12/18/2012.

   BACKGROUND INFORMATION FROM RPM LABELING REVIEW dated 6/30/2013:

   Lovaza was approved 11/10/2004 for the treatment of severe hypertriglyceridemia.

   Vascepa (icosapent ethyl) Capsules (NDA 202057) was approved 7/26/2012 for the same indication. These are the only 2 currently approved fish oil prescription products available. Following the approval of Vascepa, there were some inconsistencies noted between the package inserts of Vascepa and Lovaza, and a supplement request letter was issued to the sponsor of Lovaza on 12/18/2012, requesting some labeling revisions (letter attached). The firm responded with this labeling supplement.

   Editorial revisions were made to the labeling as well as the following sections were revised for consistency between the two labeling.

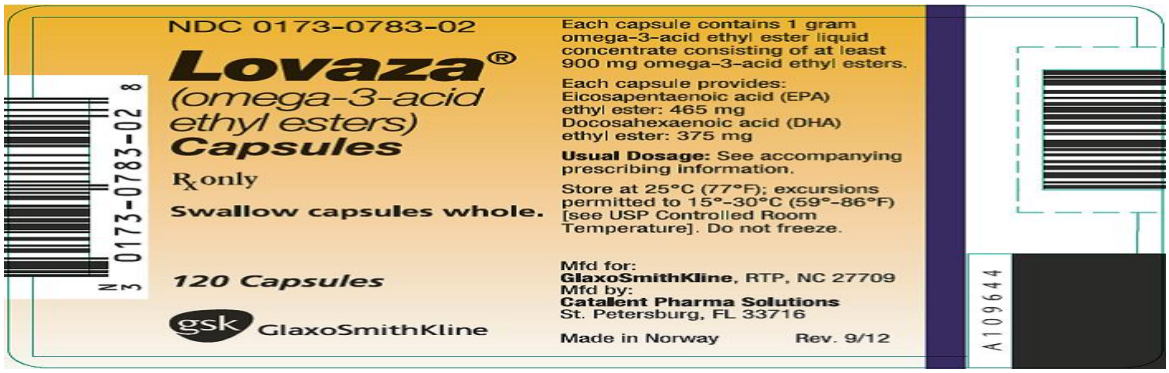
   PI

   8.3 Nursing Mothers

   Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion on the infant of a nursing mother is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. An animal study in lactating rats given oral gavage ^{14}C-ethyl EPA demonstrated that drug levels were 6 to 14 times higher in milk than in plasma.

   PPI

   "What should I tell my doctor before taking LOVAZA?
   Before you take LOVAZA, tell your doctor if you:
   ….are breastfeeding or plan to breastfeed. LOVAZA can pass into your breast milk. You and your doctor should decide if you will take LOVAZA or breastfeed."



MedWatch (checked February 26, 2014)

No new reports since new labeling approved September 2012

Lovaza (omega-3-acid ethyl esters) capsules

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)

September 2012

Summary View[1]

5 WARNINGS AND PRECAUTIONS

5.3 Recurrent Atrial Fibrillation (AF) or Flutter

- In a double-blind, placebo-controlled trial of 663 patients with symptomatic paroxysmal AF (n=542) or persistent AF (n=121), recurrent AF or flutter was observed in patients randomized to LOVAZA who received 8 grams/day for 7 days and 4 grams/day thereafter for 23 weeks at a higher rate relative to placebo. .....

- .....Although the clinical significance of these results is uncertain, there is a possible association between LOVAZA and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first 2 to 3 months of initiating therapy. LOVAZA is not indicated for the treatment of AF or flutter.

Patient Information Leaflet

What are the possible side effects of LOVAZA?

LOVAZA may cause serious side effects, including:

- increases in the frequency of a heart rhythm problem (atrial fibrillation or flutter) may especially happen in the first few months of taking LOVAZA if you already have that problem.

2. **USP -36:** (checked February 26, 2014)

   This product is the subject of a USP monograph.

   Omega-3-Acid Ethyl Esters Capsules

Revised October 2013

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature. Do not freeze. Protect from light.

• **Labeling:** The label states the amount of docosahexaenoic acid (DHA) ethyl ester and eicosapentaenoic acid (EPA) ethyl ester, and the minimum amount of total content of omega-3-acid ethyl esters in mg/Capsule. It also states the name and content of any added antioxidant.

3. **PATENT AND EXCLUSIVITY**

Patent Data – NDA 021654

No	Expiration	Use Code	Use	How filed	Labeling Impact
5656667	Apr 10, 2017	U-822	Use in Lipid Management	PIV	None

Exclusivity Data– There is no unexpired exclusivity for this product.

PATENT AMENDMENT DATED 3/18/2012

The following information was taken from the cover letter dated 3/18/2012

Based on discussions between Par and the Office of Generic Drugs ("OGD"), we understand that the administrative record for the ANDA is complete, and that there are no outstanding requests for additional data or information from OGD. The only substantive impediment to approval of the application appears to be OGD's ongoing consideration of the criteria under which it may approve a generic version of the RLD, given its composition and derivation (components obtained from the body oil of certain species of fish). There is ample administrative precedent supporting the approval of generic products referencing naturally-derived drugs that were approved through the new drug approval process, and we urge OGD to rely on this precedent in bringing its review of the ANDA to a prompt resolution. In fact, Par has a compelling need to obtain final approval of its ANDA in the very near future, as the court handling the associated paragraph IV litigation recently announced that a decision in that litigation will issue shortly. In order to position Par to market its generic product promptly upon successful resolution of the litigation – a result we expect – we respectfully request a meeting with OGD as soon as possible to identify and resolve any remaining issues associated with the approvability of the ANDA, with the goal of facilitating timely approval of the application.

We also note that Par is vested with a right to 180-day marketing exclusivity upon approval of its ANDA, notwithstanding OGD's three-year review of the application. In particular, the forfeiture provisions set forth in the federal Food, Drug and Cosmetic Act ("FDCA") indicate that there should be no forfeiture of exclusivity for the ANDA, as FDA's protracted deliberation appears to be due to the Agency's ongoing review of the requirements for approval of generic versions of the RLD.[1] Accordingly, we seek to confirm FDA's understanding that Par's hard-won right to 180-day exclusivity has not been, and will not be, forfeited as a result of OGD's drawn out review of the ANDA.

PATENT AMENDMENT DATED MARCH 24, 2011

Please be advised that an action for alleged infringement of the '077 and '667 patents was brought in the U.S. District Court for the District of Delaware ("the Delaware litigation") before the expiration of the 45 day period as described in Section 505(j)(5)(B)(iii) of the FFDCA. Please also be advised that, as a result of Par's August 05, 2010 notice, the allegations in the Delaware litigation were amended to include alleged infringement of the '488 patent.

Par certifies that sale of drug product will not begin until after expiry of the above exclusivities.

In patent amendment dated 5/1/09- Par was sued on the infringement of patents '077 and '594 in the District Court of District of Delaware.

4. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:
gelatin, glycerin, purified water and (b) (4) (shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxice, N-Butyl alcohol)

In AF dated 5/22/09, Par added the components of (b) (4) to the inactive ingredients.

In AF dated 8/24/2010 the firm listed the following inactive ingredients in the insert labeling:
gelatin, glycerol, and purified water, α-tocopherol (b) (4) mg/capsule, (components of the capsule shell), shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxide, n-butyl alcohol.

5. **MANUFACTURING FACILITY**

Emcure Pharmaceuticals USA, Inc.
21b Cotters Lane
East Brunswick, NJ 08816

[2.3.P.3- original submission]

6. **FINISHED PRODUCT DESCRIPTION**

RLD: 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

ANDA: [2.3.P.5-original submission]

(b) (4)

From labeling amendment dated 5/22/09:

e. The description of the imprint on the gelatin capsules is "P019"as indicated in the HOW SUPPLIED section of the insert. A typographical error is noted in section 2.3.P.5 of the QOS regarding the imprint of the gelatin capsules. The description of the gelatin capsules, in section 2.3.P.5 of the QOS, will be corrected and provided in an appropriate submission.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Do not freeze. KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN

8. **PRODUCT LINE**

RLD: 1 gram capsules in bottles of 120s

ANDA: The drug product will be packaged in 60s and 120s

9. **CONTAINER/CLOSURE[2.3.P.7-original submission]**

Container Closure Systems for Omega-3-Acid Ethyl Esters Capsules		
Strength	Presentation	Description of Container/Closure System
1 g	Standard Retail Bottle 60 count	(b) (4)
	Standard Retail Bottle 120 count	
	(b) (4)	
(b) (4)		

10. **PATIENT PACKAGE INSERT**

The firm provide the stand-alone PPI in amendment dated 2/19/2014

11. **BIOEQUIVALENCE/DISSOLUTION:** Bio Review inadequate as of review date 6/12/2013.

12. **SPL DATA ELEMENTS**

ANDA data submitted in amendment dated 8/23/2010

ANDA:
Omega-3-Acid Ethyl Esters, 1 gram
Color yellow ((pale yellow)); Score no score; Shape OVAL; Size 4mm; Imprint Code P; 019

We will ask the firm to revise the strength to read "Omega-3-Acid Ethyl Esters, 900 mg" rather than "Omega-3-Acid Ethyl Esters, 1 g." in the SPL data elements.

Amendment dated 2/19/2014 the firm submitted revised strength in the SPL (see below):

Revised October 2013

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
OMEGA-3-ACID ETHYL ESTERS (OMEGA-3 FATTY ACIDS)	OMEGA-3-ACID ETHYL ESTERS	900 mg

RLD:
900 mg Omega-3-Acid Ethyl Esters
Color YELLOW (light yellow); Score no score; Shape CAPSULE; Size 24mm; Imprint Code LOVAZA

13. **EXPRESSION OF STRENGTH:**

There is a Citizen Petition memorandum available under the RLD regarding the expression of strength dated January 23, 2014.

The Office of Regulatory Policy (ORP) has requested a consult on the citizen petition submitted by John H. Fuson, Crowell & Moring, LLP, on February 6, 2013 (Petition FDA-2013-P-0148): However, given the prior practice for other naturally-sourced mixtures, it is not unreasonable to maintain the status quo of designating the entire fish oil mixture as the active ingredient with a strength of 1 g, as was concluded by the Center Director in the November 18, 2013 Center Director Decisional Briefing.

Agency letter dated 6/18/12 for NDA 021654:
According to Lovaza's approved specification, each capsule contains from 950 mg to 1050 mg of esterified purified fish oil. The principal components are two omega-3 acid ethyl esters, eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester. Both are required to be present at a combined concentration of between 800 and 880 mg/capsule. The drug substance specification also includes an acceptance criterion of at least 90% (w/w) total omega-3 ethyl esters – the active ingredients.

Recently reviewed data from your NDA indicate that the total omega-3 ethyl esters content does not deviate significantly from 90% of total capsule fill. For the target 1 gram capsule fill, this amounts to 900 mg of omega-3 ethyl esters. Consequently, we believe that the labeled strength should be changed from 1 gram to 900 mg.

Please revise all labeling to reflect a strength per capsule of 900 mg.

NDA sponsor response dated 8/6/2012:
GSK is not in agreement that the labeled strength of LOVAZA should be changed to 900 mg (see **Attachment 1** for details).

GSK proposes to revise the Dosage Forms and Strengths section of the Prescribing Information to incorporate the language that is currently used on the trade and sample container packaging:
• Each capsule contains 1 gram omega-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.
This change to the Prescribing Information would afford a consistent description of the product (in the PI and on the container labels) and would alleviate any potential misunderstandings regarding the amount of active ingredient in a 1 gram capsule. Division consideration and concurrence with this proposal would be much appreciated.

The attachment provided by the firm in the 8/6/2012 amendment provides a detailed explanation of the inactive ingredients.

Email from TL's regarding expression of strength dated 5/7/2013

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 07, 2013 3:29 PM
To: Turner, Betty
Subject: FW: Strength on PDP (Omega-3)

From: Lee, Koung U
Sent: Tuesday, May 07, 2013 2:36 PM
To: Golson, Lillie D; Wu, Ruby (Chi-Ann)
Subject: RE: Strength on PDP (Omega-3)

I agree. What if the RLD gets approved with a different strength?

From: Golson, Lillie D
Sent: Tuesday, May 07, 2013 2:09 PM
To: Wu, Ruby (Chi-Ann); Lee, Koung U
Cc: Golson, Lillie D
Subject: RE: Strength on PDP (Omega-3)

I believe the strength should appear on the PDP as we do with all our products. All vitamins that I buy do have the strength. Might even be better to express as mg rather than grams. There are many others on google image.

<< File: images[2].jpg >> << File: images[1].jpg >> << File: images[3].jpg >>

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 07, 2013 1:18 PM
To: Lee, Koung U; Golson, Lillie D
Subject: Strength on PDP (Omega-3)

Hi Lillie and Koung,

What do you think about the following situation….

RLD Label: (strength not specified on the PDP)

<< File: image[10].jpg >>

OSE review dated 4/27/2004 for the RLD

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

The request for the strength on the PDP seemed to have stopped there.

What are your thoughts….should we be the same as the RLD and remain silent on the strength or ask the firm to include the strength "1 gram*" on the PDP pursuant to the Guidance for Industry?

The **principal display panel** (PDP) is the panel of a label that is most likely to be displayed, presented, shown, or examined by the end user. We recommend that the PDP include the following critical information:

- Proprietary name
- **Established name** or **proper name**
- Product strength
- Route(s) of administration
- Warnings (if any) or cautionary statements (if any)

What are your thoughts?

Ruby

From: Turner, Betty
Sent: Tuesday, May 07, 2013 1:02 PM
To: Wu, Ruby (Chi-Ann)
Subject: RE: ANDA (b) (4)

Hi Ruby,

I like having the strength on the PDP, but would we be following the RLD or is that difference allowed? I do not have a problem with asking the firm to include the strength on the PDP. Do you know of other cases like this?

(b) (4)

If we put the 1 gm on the PDP, I think we will need the asterisk because it consist of at least 900 mg Omega-3-acid ethyl esters.

No rush. Any time is fine with me.

Thanks,
Betty

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 07, 2013 12:41 PM
To: Turner, Betty
Subject: RE: ANDA (b) (4)

Hi Betty,

OSE review dated 4/27/2004

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

However, I can't find the amendment where the firm responded to this request.

Personally, I do not see a reason why we shouldn't include the strength. Maybe we can do a "Upon further consideration, we encourage you to include the expression of strength on the principal display panel."

Do you think we need an asterisk after "1 gram*" and before the "Each capsule contains" statement?

What do you think?

Ruby

P.S. I just started my review so probably won't send it back to you until tomorrow.

14. **EASILY CORRECTABLE LABELING DEFICIENCIES AMENDMENT dated 2/19/2014;**

The following information was taken from the cover letter dated 2/19/2014:

Par's labeling has been updated to be in line with the 09/11/2013 approved labeling of the reference listed drug, LOVAZA. The Container Labels, Physician Insert and Patient Information Leaflet have been further revised according to the Agency's recommendations listed in the Easily Correctable Deficiency dated 02/07/2014.

In response to comment 3 d. Description: Par confirms that the following statement accurately reflects our drug product: These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).

15. **Firms response to labeling amendment dated 11/19/2009**

Revised October 2013

Labeling comment:
GENERAL COMMENT:
We note that you do not have "α-tocopherol" listed as an inactive ingredient. However, in 2.3.P.5 (original submission), the content of α-tocopherol is stated as (b) (4) mg/capsule. Please explain this discrepancy.

Firm's Response
The content of "α-tocopherol" was inadvertently omitted from the listing of inactive ingredients in the insert. The content of α-tocopherol as (b) (4) mg/capsule is now listed as an inactive ingredient in the insert.

INSERT
Please revise your insert in accordance to the most recently approved RLD labeling (21654/S-022; approved 9/16/09. We refer you to Drugs@FDA website.

Firm's Response
Our insert has been revised in accordance to the most recently approved 9/16/09, RLD labeling.

The patient package insert has also been updated to be in line with the most recently approved RLD labeling.

Date of Review:	February 26, 2014
Primary Reviewer:	Betty Turner
Team Leader:	Chi-Ann Wu

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BETTY B TURNER
02/27/2014

CHI-ANN Y WU
02/27/2014
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	091018
Date of Submission:	February 9, 2010 and August 24, 2010
Applicant's Name:	Par Pharmaceutical, Inc.
Established Name and Strength:	Omega-3-Acid Ethyl Esters Capsules USP, 1 gram

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Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☒ Easily correctable (respond within 10 business days)

☐ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on August 13, 2013 based on your submission dated February 9, 2010 and August 24, 2010:

1. GENERAL COMMENT:
   This product is the subject of a USP monograph. We encourage you to add "USP" to the established name in the container labels and insert labeling.

2. CONTAINER
   a. Please revise the expression of strength to read "1 gram*" add an asterisk immediately before the "*Each capsule contains…" statement on the side panel.

   b. Add "Protect from light" to the storage statement.

   c. Add "Swallow capsules whole" on the principal display panel.

   d. Please decrease the prominence of the net quantity statement.

3. PHYSICIAN INSERT

a. GENERAL COMMENTS:

i. Due to changes in the insert labeling for the reference listed drug Lovaza® (omega-3-acid ethyl esters) Capsules by GlaxoSmithKline, (NDA 021654/S-037) approved June 26, 2013, please revise your labeling to be in accordance with the reference listed drug labeling. If you are unable to obtain this labeling at the Drugs@FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm), please contact the labeling reviewer, Betty Turner (betty.turner@fda.hhs.gov).

ii. The Agency recommends two-column format for the "HIGHLIGHTS" and "CONTENTS" sections. Please revise.

b. HIGHLIGHTS, Title: Please also include the route of administration (refer to 21 CFR 201.57 (a)(2)).

c. Please insert a horizontal line to separate the information in HIGHLIGHTS OF PRESCRIBING INFORMATION section, from the FULL PRESCRIBING INFORMATION: CONTENTS* section and also the FULL PRESCRIBING INFORMATION section (refer to 21 CFR 201.57 (d) (2)).

d. DESCRIPTION: Please confirm if the following statement accurately reflects your drug product: These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA- approximately 465 mg) and docosahexaenoic acid (DHA- approximately 375 mg).

e. HOW SUPPLIED/STORAGE AND HANDLING: Please add "Protect from light" to the storage statement.

4. PATIENT INFORMATION LEAFLET

a. Please provide the stand-alone patient information leaflet for our review.

b. Please ensure that your leaflet is in accordance with the RLD approved on June 26, 2013.

5. SPL

a. In the data elements, revise the strength to read "Omega-3-Acid Ethyl Esters, 900 mg" rather than "Omega-3-Acid Ethyl Esters, 1 g."

b. Please update to be in accordance with the RLD approved on June 26, 2013.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required?

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☐ n/a

	Date submitted	Final or Draft	Recommendation
CONTAINER Bottles of 60's and 120s	5/22/2009	Draft	Revision requested
INSERT	8/24/2010	Draft	Revision requested
PATIENT INFORMATION	8/24/2010	Draft	Revision requested

REVISIONS NEEDED POST APPROVAL?

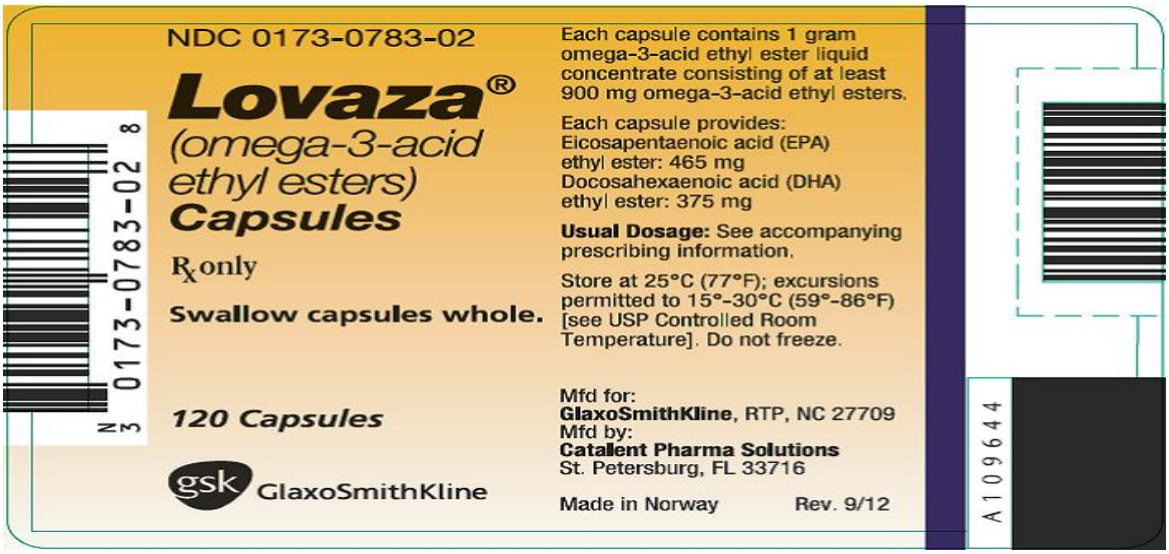
NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

FOR THE RECORD: Please note the first 2 review cycles were completed by labeling reviewer Thuyanh Vu. Portions of this review were taken from the review dated 11/18/2009 in DARRTS.

1. **MODEL LABELING:** This review is based on the labeling for Lovaza® (omega-3-acid ethyl esters) Capsule of SmithKline Beecham, NDA 021654/S-037; approved June 26, 2013.

   S-022 provided for PLR format and inclusion of atorvastatin and rosuvastatin in the Drug Interactions subsection.

   S-014, approved on 11/7/07 provided for the revised patient package insert.



   This is a first generic drug.

2. **USP-36:** (checked August 13, 2013)
   Omega-3-Acid Ethyl Esters Capsules
   ADDITIONAL REQUIREMENTS
   - Packaging and Storage: Preserve in tight containers, and store at controlled room temperature. Do not freeze. Protect from light.
   - Labeling: The label states the amount of docosahexaenoic acid (DHA) ethyl ester and eicosapentaenoic acid (EPA) ethyl ester, and the minimum amount of total content of omega-3-acid ethyl esters in mg/Capsule. It also states the name and content of any added antioxidant.

3. **PATENT AND EXCLUSIVITY** (checked August 13, 2013)

Patent Data – NDA 021654

No	Expiration	Use Code	Use	**How filed**	**Labeling Impact**
5502077	Mar 26, 2013	U-822	Use In Lipid Management	PIV	None
5656667	Apr 10, 2017	U-822	Use in Lipid Management	PIV	None
5698594	Aug 4, 2009	U-822	Use In Lipid Management	PIII	Expired
7732488	Jan 30, 2025			PIV	None

Exclusivity Data– NDA 021654

Code	Reference	Expiration	**Labeling impact**
M-87	Inclusion of results from two drug interaction studies with Lipid and Crestor in Clinical Pharmacology section	Sep 16, 2012	**None Expired**

PATENT AMENDMENT DATED MARCH 24, 2011

Please be advised that an action for alleged infringement of the '077 and '667 patents was brought in the U.S. District Court for the District of Delaware ("the Delaware litigation") before the expiration of the 45 day period as described in Section 505(j)(5)(B)(iii) of the FFDCA. Please also be advised that, as a result of Par's August 05, 2010 notice, the allegations in the Delaware litigation were amended to include alleged infringement of the '488 patent.

Par certifies that sale of drug product will not begin until after expiry of the above exclusivities.

In patent amendment dated 5/1/09- Par was sued on the infringement of patents '077 and '594 in the District Court of District of Delaware.

4. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:
gelatin, glycerin, purified water and (b) (4) (shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxice, N-Butyl alcohol)

In AF dated 5/22/09, Par added the components of (b) (4) to the inactive ingredients.

In AF dated 8/24/2010 the firm listed the following inactive ingredients in the insert labeling:
gelatin, glycerol, and purified water, α-tocopherol (b) (4) mg/capsule, (components of the capsule shell), shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxide, n-butyl alcohol.

5. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
   Emcure Pharmaceuticals USA, Inc.
   21b Cotters Lane
   East Brunswick, NJ 08816

   [2.3.P.3- original submission]

6. **FINISHED PRODUCT DESCRIPTION**

   RLD: 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

   ANDA: [2.3.P.5-original submission]

   Pale yellow, clear, oval soft gelatin capsules imprinted "019" with white ink.

   From labeling amendment dated 5/22/09:

> e. The description of the imprint on the gelatin capsules is "P019"as indicated in the HOW SUPPLIED section of the insert. A typographical error is noted in section 2.3.P.5 of the QOS regarding the imprint of the gelatin capsules. The description of the gelatin capsules, in section 2.3.P.5 of the QOS, will be corrected and provided in an appropriate submission.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

   RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

   ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Do not freeze. KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN

8. **PRODUCT LINE**

   RLD: 1 gram capsules in bottles of 120s

   ANDA: The drug product will be packaged in 60s and 120s

9. **CONTAINER/CLOSURE: [2.3.P.7-original submission]**

Container Closure Systems for Omega-3-Acid Ethyl Esters Capsules		
Strength	Presentation	Description of Container/Closure System
1 g	Standard Retail Bottle 60 count	(b) (4)
	Standard Retail Bottle 120 count	(b) (4)
	(b) (4)	

10. **PATIENT PACKAGE INSERT**
The firm did not provide the stand-alone PPI. We will ask the firm to submit for our review.

11. **BIOEQUIVALENCE/DISSOLUTION:** Bio Review inadequate as of review date 6/12/2013.

12. **SPL DATA ELEMENTS**
ANDA data submitted in amendment dated 8/23/2010

RLD:
900 mg Omega-3-Acid Ethyl Esters
Color YELLOW (light yellow); Score no score; Shape CAPSULE; Size 24mm; Imprint Code LOVAZA

ANDA:
Omega-3-Acid Ethyl Esters, 1 gram
Color yellow ((pale yellow)); Score no score; Shape OVAL; Size 4mm; Imprint Code P; 019

We will ask the firm to revise the strength to read "Omega-3-Acid Ethyl Esters, 900 mg" rather than "Omega-3-Acid Ethyl Esters, 1 g."

13. **EXPRESSION OF STRENGTH:**
Agency letter dated 6/18/12 for NDA 021654:
According to Lovaza's approved specification, each capsule contains from 950 mg to 1050 mg of esterified purified fish oil. The principal components are two omega-3 acid ethyl esters, eicosapentaenoic acid (EPA) ethyl ester and docosahexaenoic acid (DHA) ethyl ester. Both are required to be present at a combined concentration of between 800 and 880 mg/capsule. The drug substance specification also includes an acceptance criterion of at least 90% (w/w) total omega-3 ethyl esters – the active ingredients.

Recently reviewed data from your NDA indicate that the total omega-3 ethyl esters content does not deviate significantly from 90% of total capsule fill. For the target 1 gram capsule fill, this amounts to 900 mg of omega-3 ethyl esters. Consequently, we believe that the labeled strength should be changed from 1 gram to 900 mg.

Please revise all labeling to reflect a strength per capsule of 900 mg.

NDA sponsor response dated 8/6/2012:
GSK is not in agreement that the labeled strength of LOVAZA should be changed to 900 mg (see **Attachment 1** for details).

GSK proposes to revise the Dosage Forms and Strengths section of the Prescribing Information to incorporate the language that is currently used on the trade and sample container packaging:
• Each capsule contains 1 gram omega-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.
This change to the Prescribing Information would afford a consistent description of the product (in the PI and on the container labels) and would alleviate any potential misunderstandings regarding the amount of active ingredient in a 1 gram capsule. Division consideration and concurrence with this proposal would be much appreciated.

The attachment provided by the firm in the 8/6/2012 amendment provides a detailed explanation of the inactive ingredients.

Email from TL's regarding expression of strength dated 5/7/2013

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 07, 2013 3:29 PM
To: Turner, Betty
Subject: FW: Strength on PDP (Omega-3)

From: Lee, Koung U
Sent: Tuesday, May 07, 2013 2:36 PM
To: Golson, Lillie D; Wu, Ruby (Chi-Ann)
Subject: RE: Strength on PDP (Omega-3)

I agree. What if the RLD gets approved with a different strength?

From: Golson, Lillie D
Sent: Tuesday, May 07, 2013 2:09 PM
To: Wu, Ruby (Chi-Ann); Lee, Koung U
Cc: Golson, Lillie D
Subject: RE: Strength on PDP (Omega-3)

I believe the strength should appear on the PDP as we do with all our products. All vitamins that I buy do have the strength. Might even be better to express as mg rather than grams. There are many others on google image.

<< File: images[2].jpg >> << File: images[1].jpg >> << File: images[3].jpg >>

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 07, 2013 1:18 PM
To: Lee, Koung U; Golson, Lillie D
Subject: Strength on PDP (Omega-3)

Hi Lillie and Koung,

What do you think about the following situation….

RLD Label: (strength not specified on the PDP)

<< File: image[10].jpg >>

OSE review dated 4/27/2004 for the RLD

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

The request for the strength on the PDP seemed to have stopped there.

What are your thoughts….should we be the same as the RLD and remain silent on the strength or ask the firm to include the strength "1 gram*" on the PDP pursuant to the Guidance for Industry?

The **principal display panel** (PDP) is the panel of a label that is most likely to be displayed, presented, shown, or examined by the end user. We recommend that the PDP include the following critical information:

- Proprietary name
- **Established name** or **proper name**
- Product strength
- Route(s) of administration
- Warnings (if any) or cautionary statements (if any)

What are your thoughts?

Ruby

From: Turner, Betty
Sent: Tuesday, May 07, 2013 1:02 PM
To: Wu, Ruby (Chi-Ann)
Subject: RE: ANDA (b) (4)

Hi Ruby,

I like having the strength on the PDP, but would we be following the RLD or is that difference allowed? I do not have a problem with asking the firm to include the strength on the PDP. Do you know of other cases like this?

(b) (4)

If we put the 1 gm on the PDP, I think we will need the asterisk because it consist of at least 900 mg Omega-3-acid ethyl esters.

No rush. Any time is fine with me.

Thanks,
Betty

From: Wu, Ruby (Chi-Ann)
Sent: Tuesday, May 07, 2013 12:41 PM
To: Turner, Betty
Subject: RE: ANDA (b) (4)

Hi Betty,

OSE review dated 4/27/2004

CONTAINER LABEL

The product strength should appear immediately following or below the established name and be more prominent on the label.

The comment was sent to the firm on 6/4/2004.

However, I can't find the amendment where the firm responded to this request.

Personally, I do not see a reason why we shouldn't include the strength. Maybe we can do a "Upon further consideration, we encourage you to include the expression of strength on the principal display panel."

Do you think we need an asterisk after "1 gram*" and before the "Each capsule contains" statement?

What do you think?

Ruby

P.S. I just started my review so probably won't send it back to you until tomorrow.

14. **Firms response to labeling amendment dated 11/19/2009**

Labeling comment:

GENERAL COMMENT:

We note that you do not have "α-tocopherol" listed as an inactive ingredient. However, in 2.3.P.5 (original submission), the content of α-tocopherol is stated as (b) (4) mg/capsule. Please explain this discrepancy.

Firm's Response

The content of "α-tocopherol" was inadvertently omitted from the listing of inactive ingredients in the insert. The content of α-tocopherol as (b) (4) mg/capsule is now listed as an inactive ingredient in the insert.

INSERT

Please revise your insert in accordance to the most recently approved RLD labeling (21654/S-022; approved 9/16/09. We refer you to Drugs@FDA website.

Firm's Response
Our insert has been revised in accordance to the most recently approved 9/16/09, RLD labeling.

The patient package insert has also been updated to be in line with the most recently approved RLD labeling.

15. Amendment dated 8/24/2010 was submitted in response to the telephone conversation of August 6, 2010 with Ann Vu, labeling reviewer.

Based on our telephone conversation with Ann Vu, Par's labeling, updated to exclude reference to Atorvastatin (Lipitor) and Rosuvastion (Crestor) in the Clinical Phamacology Section under the Drug-Drug Interaction subsection due to SmithKline Beecham exclusivity for M-87, and in view of 21 CFR 314.94(a)(8)(iv), will be acceptable.

Date of Review: August 13, 2013

Primary Reviewer: Betty Turner

Team Leader: Chi-Ann Wu

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/s/

BETTY B TURNER
08/16/2013

CHI-ANN Y WU
08/16/2013
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-018 Date of Submission: May 22, 2009
Applicant's Name: Par Pharmaceutical Inc.
Established Name: Omega 3-Acid Ethyl Esters Capsule, 1 gram

Labeling Deficiencies:

1. GENERAL COMMENT:

We note that you do not have "α-tocopherol" listed as an inactive ingredient. However, in 2.3.P.5-(original submission), the content of α-tocopherol is stated as (b) (4) mg/capsule. Please explain this discrepancy.

2. **CONTAINER**: (60's, 120's)

Acceptable in final print.

3. **INSERT:**

Please revise your insert in accordance to the most recently approved RLD labeling (21654/S-022; approved 9/16/09). We refer you to Drugs@FDA website.

4. **PATIENT PACKAGE INSERT:**

Please see INSERT comment.

Submit final printed labeling electronically. We refer you to the http://www.fda.gov/oc/datacouncil/spl.html website for guidance.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

NOTES/QUESTIONS TO THE CHEMIST:

Sent email to Suhas on November 12, 2009:

Note that the RLD and Apotex's ANDA 90-973 has this statement in the labeling and is part of the manufacturing process: Inactive ingredients: 4 mg α-tocopherol (in a carrier of soybean oil).

Are Par's capsules equivalent to the RLD's and Apotex's capsules without the a-Tocopherol?

However, in the 2.3.P.5 of the QOS, Par noted that each capsule contains (b) (4) mg/capsule of a-Tocopherol. I do not know how or when the a-Tocopherol was added.

Another concern is that α-tocopherol (a form of Vitamin E) itself could provide some antioxidant and cardio protection. Not sure how much α-tocopherol exerts its effects on the omega 3 effects itself. If Par's product does not contain α-tocopherol, then would it exert the same anti-lipid effect as the RLD?

I'll send out a comment to Apotex about the a-Tocopherol in the 2.3.P.5 section.

Thanks
Ann

FOR THE RECORD:

1. MODEL LABELING: This review was based on the labeling for Lovaza of Smithkline Beecham (021654/S-022, approved on 9/16/09). S-022 provided for drug interaction information between rosuvastatin and atorvastatin and conversion of PI fomat to PLR.

This is a first generic drug.

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 21-654

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5502077	Mar 26, 2013	U-822	Use in Lipid Management	IV	
5656667	Apr 10, 2017	U-822	Use in Lipid Management	IV	
5698594	Aug 4, 2009	U-822	Use in Lipid Management	III	

Exclusivity-Data – NDA 21-654

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021654	**001**	**M-64**	**Jun 12, 2010**
021654	**001**	**NCE**	**Nov 10, 2009**

Par certifies that sale of drug product will not begin until after expiry of the above exclusivities.

In patent amendment dated 5/1/09- Par was sued on the infringement of patents '077 and '594 in the District Court of District of Delaware.

3. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:

gelatin, glycerin, purified water and [redacted] (b) (4) (shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxice, N-Butyl alcohol)

In AF dated 5/22/09, Par added the components of [redacted] (b) (4) to the inactive ingredients.

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Emcure Pharmaceuticals USA, Inc.
21b Cotters Lane
East Brunswick, NJ 08816

[2.3.P.3- original submission]

5. FINISHED DOSAGE FORM

NDA: transparent soft gelatin capsules filled with light-yellow oil and bearing the designation REL900

ANDA: [2.3.P.5-original submission]

Pale yellow, clear, oval soft gelatin capsules imprinted "019" with white ink.

From labeling amendment dated 5/22/09:

e. The description of the imprint on the gelatin capsules is "P019"as indicated in the HOW SUPPLIED section of the insert. A typographical error is noted in section 2.3.P.5 of the QOS regarding the imprint of the gelatin capsules. The description of the gelatin capsules, in section 2.3.P.5 of the QOS, will be corrected and provided in an appropriate submission.

6. CONTAINER/CLOSURE:

[2.3.P.7-original submission]

Container Closure Systems for Omega-3-Acid Ethyl Esters Capsules		
Strength	Presentation	Description of Container/Closure System
1 g	Standard Retail Bottle 60 count	(b) (4)
	Standard Retail Bottle 120 count	
		(b) (4)
	(b) (4)	

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- Not USP: Checked on April 15, 2009)
- RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.
- ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Do not freeze. KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN

8. SCORING

N/A

9. PACKAGE CONFIGURATION

- RLD: 1 gram capsules in bottles of 60s and 120s
- ANDA: The drug product will be packaged in 60's, and 120's

Date of Review: November 12, 2009 **Date of Submission:** May 22, 2009

Primary Reviewer: Thuyanh Vu **Date:**

Team Leader: John Grace **Date:**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91018	ORIG-1	PAR PHARMACEUTICAL	OMEGA-3-ACID ETHYL ESTERS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
11/12/2009

JOHN F GRACE
11/18/2009

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-018 Date of Submission: November 10, 2008
Applicant's Name: Par Pharmaceutical Inc.
Established Name: Omega 3-Acid Ethyl Esters Capsule, 1 gram

Labeling Deficiencies:

1. **CONTAINER**: (60's, 120's)
   a. The manufacturer of this product is Emcure, yet there is no mention of Emcure on the labels. According to 21 CFR 201.1(h)(2), "The appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer of the product. That representation is false and misleading, and the drug product is misbranded under section 502(a) of the act, if the person is not the manufacturer of the product in accordance to this section". Please revise your labels by adding "Distributed by Par..." or "Manufactured by Emcure..."

   b. We encourage adding the statement "Pharmacist: please dispense with patient package insert".

2. **INSERT:**
   a. Please add "Rx only" to appear directly below the title of the insert.

   b. DESCRIPTION: Please add the components of the (b) (4) to your list of inactive ingredients.

   c. CLINICAL STUDIES: The subjection "Very High Triglycerides: (b) (4) from your proposed labeling. Please refer to the RLD.

   d. PRECAUTIONS: Revise the "Pregnancy" subsection to read:

   (b) (4)

   Pregnancy Category C

   e. In section 2.3.P.5 of the QOS, the gelatin capsules were imprinted with "019" while the HOW SUPPLIED section described the capsules imprinted with "P019". Please clarify.

3. **PATIENT PACKAGE INSERT:**
   Please see INSERT comment b.

Submit final printed labeling electronically. We refer you to the http://www.fda.gov/oc/datacouncil/spl.html website for guidance.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

NOTES/QUESTIONS TO THE CHEMIST:

Note that the RLD and Apotex's ANDA 90-973 has this statement in the labeling and is part of the manufacturing process: Inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil). Apotex only references the carrier of soybean oil.

Is this possible that all of the two companies and the RLD has the inactive ingredient as α-tocopherol while Par's does not. Are the capsules truly equivalent?

However, in the 2.3.P.5 of the QOS, Par noted that each capsule contains (b) (4) mg/capsule of a-Tocopherol. I do not know how or when the a-Tocopherol was added.

Another concern is that α-tocopherol (a form of Vitamin E) itself could provide some antioxidant and cardio protection. Not sure how much α-tocopherol exerts its effects on the omega 3 effects itself. If Par's product does not contain α-tocopherol, then would it exert the same anti-lipid effect as the RLD?

Currently, this ANDA is assigned to a random chemist.

FOR THE RECORD:

1. **MODEL LABELING:** This review was based on the labeling for Lovaza of Smithkline Beecham (S-021, approved on 6/3/08). S-021 provided the change of the proprietary from Omacor to Lovaza. S-014, approved on 11/7/07 provided for the revised patient package insert.

   This is a first generic drug.

2. **PATENTS/EXCLUSIVITIES**

   Patent Data – NDA 21-654

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5502077	Mar 26, 2013	U-822	Use in Lipid Management	IV	
5656667	Apr 10, 2017	U-822	Use in Lipid Management	IV	
5698594	Aug 4, 2009	U-822	Use in Lipid Management	III	

   Exclusivity-Data – NDA 21-654

		Exclusivity Data	
Appl No	**Prod No**	**Exclusivity Code**	**Exclusivity Expiration**
021654	**001**	**M-64**	**Jun 12, 2010**
021654	**001**	**NCE**	**Nov 10, 2009**

   Par certifies that sale of drug product will not begin until after expiry of the above exclusivities.

3. **INACTIVE INGREDIENTS**

There appears to be a discrepancy in inactives between the DESCRIPTION and the composition statement. [2.3.P.1-original submission]

Inactive ingredients:

gelatin, glycerin, purified water and (b) (4) (shellac glaze, isopropyl alcohol, simethicone, titanium dioxide, propylene glycol, ammonium hydroxice, N-Butyl alcohol)

See comment to Par about adding the components of (b) (4) to the list of inactive ingredients.

Note that the RLD and Apotex's ANDA 90-973 has this statement in the labeling and is part of the manufacturing process: Inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil). Apotex only references the carrier of soybean oil.

4. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

Emcure Pharmaceuticals USA, Inc.
21b Cotters Lane
East Brunswick, NJ 08816

[2.3.P.3- original submission]

See comment to firm about discrepancy between drug product manufacturer.

5. **FINISHED DOSAGE FORM**

NDA: transparent soft gelatin capsules filled with light-yellow oil and bearing the designation REL900

ANDA: [2.3.P.5-original submission]

Pale yellow, clear, oval soft gelatin capsules imprinted "019" with white ink.

6. **CONTAINER/CLOSURE:**
[2.3.P.7-original submission]

Container Closure Systems for Omega-3-Acid Ethyl Esters Capsules		
Strength	Presentation	Description of Container/Closure System
1 g	Standard Retail Bottle 60 count	(b) (4)
	Standard Retail Bottle 120 count	
		(b) (4)
	(b) (4)	

7. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- Not USP: Checked on April 15, 2009)
- RLD: Stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze.
- ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Do not freeze. KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN

8. **SCORING**

N/A

9. **PACKAGE CONFIGURATION**

- RLD: 1 gram capsules in bottles of 60s and 120s

- ANDA: The drug product will be packaged in 60's, and 120's

Date of Review: April 16, 2009	**Date of Submission:** November 10, 2008
Primary Reviewer: Thuyanh Vu	**Date:**
Team Leader: John Grace	**Date:**

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/s/

Thuyanh Vu
4/16/2009 12:20:21 PM
LABELING REVIEWER

John Grace
4/21/2009 12:07:08 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91018

CHEMISTRY REVIEWS

CMC Acceptable

Addendum # 1 to ANDA 91018 Review# 04

Omega-3-acid ethyl esters capsule USP, 1 g

Par Pharmaceuticals Inc.

MA Rahman, PhD
Office of Generic Drugs
Division of Chemistry III

Background:

The CMC of this ANDA 91018 for Omega-3 acid ethyl esters capsules USP, 1 g was found adequate per review # 4 Darrts dated 06/04/2014. This addendum # 1 is generated in response to firm's amendment dated June 04, 2014 for the revision of drug substance specification to be consistent with the API holder's specification for Omgea-3-acid ethyl esters API. Firm states that the specifications of the following tests parameters are updated based on the recommendation of the DMF holder.

(b) (4)

Following this page, 4 Pages Withheld in Full as (b)(4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MD A RAHMAN
06/19/2014

LEIGH A SEARS
06/19/2014

LAXMA R NAGAVELLI
06/19/2014

VILAYAT A SAYEED
06/19/2014

CHEMISTRY REVIEW

A. Check List *(once you check "yes" in the checklist on top, skip the rest afterward):*

- First Generic? Yes: ☐ No: ☒
- MR Product? Yes: ☐ No: ☒
- Solid IR RPN > 60 or Inj. Q1/Q2 ≠ RLD? Yes: ☐ No: ☒
- Major Formulation/ Mfg. Process Change? Yes: ☒ No: ☐

B. Review Requirement: **3 Tier:** ☒ **2 Tier:** ☐

C. Approvability: – ***CMC Acceptable***

First Generic: No
CMC: Acceptable
Labeling: Adequate
EES: Acceptable
Bio: Adequate

ANDA 91018

Omega-3-acid ethyl esters capsules, 1 gm

PAR Pharmaceutical Inc.

M A Rahman
Team 34
Division of Chemistry III
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #:** 91018

2. **REVIEW #:** R04

3. **REVIEW DATE:** 05/06/2014

4. **REVIEWER:** M A Rahman, PhD

5. **PREVIOUS DOCUMENTS: N/A**

Previous Document(s)	Document Date
Original ANDA	November 10, 2008
Amendment	October 14, 2009
Amendment	February 12, 2010
Gratuitous Amendment	March 02, 2010
Amendment	September 28, 2011
Correspondence	March 17, 2011
Amendment	December 07, 2011
Correspondence	May 15, 2012
Patent amendment	May 18, 2012
Amendment	Nov 1, 2013 (Letter 10/31/2013)

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Amendment	April 14, 2014

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Par Pharmaceutical Inc.
Address:	One Ram Ridge Road, Spring Valley, NY 10977
Representative:	Janis Picurro, Director, Regulatory Affairs
Telephone:	845-425-7100
Fax:	845-573-5795

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: N/A

Non-Proprietary Name (USAN): Omega-3-Acid Ethyl Esters Capsules, 1 gm

9. LEGAL BASIS FOR SUBMISSION:

This ANDA # 91018 of Omega-3-Acid Ethyl Esters Capsules, 1 gm is being submitted based on the reference listed drug (RLD): Lovaza® Capsules (Omega-3-Acid Ethyl Esters Capsules, 1 gm) is approved for GlaxoSmithKline (NDA 21654).

The following United States Patents is/are listed in "Electronic Orange Book" (*Approved Drug Products with Therapeutic Equivalence Evaluations* for the above-identified RLD:

1.3.5.1.-1 Patents Listed for the Reference Listed Drug			
Application Number	**Patent Number**	**Patent Expiration**	**Use Code**
021654	5502077	March 26, 2013	U-822
021654	5656667	August 27, 2018	U-822
021654	5698594	August 4, 2009	U-822

Par submits the following certifications to these patents:

The below table lists all certifications provided herein, addressing Section 505(j)(2)(A) of the FD&C Act. Certifications outlined in the table below are provided on the following pages.

Table 1.3.5.2-1 List of Applicable Certifications		
Patent Number	**Certification**	**Expiration (PED*, if applic.)**
5502077	Paragraph IV	March 26, 2013
5656667	Paragraph IV	August 27, 2018
5698594	Paragraph IV	August 4, 2009

*PED – patent expiration extended due to pediatric exclusivity (only if applicable)

Please refer to Section 1.12.11 for the relevant "Electronic Orange Book" pages.

Pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, Par Pharmaceutical Inc. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 7,732,488 is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of 1 g capsules of omega-3-acid ethyl esters, for which this application is submitted. Par Pharmaceutical Inc. previously submitted certifications pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act with respect to U.S. Patent No. 5,502,077 and U.S. Patent No. 5,656,667. Par Pharmaceutical Inc. does not amend, withdraw, or alter those previously submitted certifications.

10. PHARMACOL. CATEGORY: Triglyceride reducing agent

11. DOSAGE FORM: Capsules (Soft Gelatin)

12. STRENGTH/POTENCY: 1 gm (MDD = 4 gm)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X___Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__X__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Omega-3 acid ethyl esters (b) (4) is a fish-oil fatty acid ester concentrate containing the followings:

Chemical Name for EPA:

• Eicosapentaenoic acid

Chemical Name for DHA:

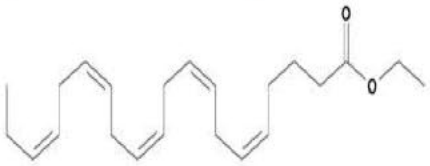
Docosahexaenoic acid

CAS #: 91051-05-7

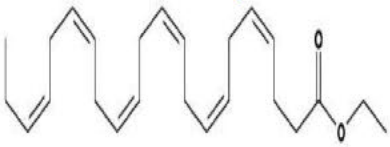
United States Adopted Name (USAN): Omega-3-Acid Ethyl Esters

International Non-Proprietary Name (INN): Omega-3-Acid Ethyl Esters (b) (4)

Structure for EPA-EE (Eicosapentaenoic Acid Ethyl Ester):



Structure for DHA-EE (Docosahexaenoic acid Ethyl Ester):



Molecular Formula:

• EPA-EE – $C_{22}H_{34}O_2$

• DHA-EE – $C_{24}H_{36}O_2$

Molecular Weight:

• EPA-EE – 330.51

• DHA-EE – 356.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	**Adequate**	05/23/2014	Reviewed by MA Rahman
	III			3			
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* number to be assigned

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	01/21/2014	T. Sharp
Methods Validation	N/A		
Labeling	Adequate	4/24/2014	B. Turner
Bioequivalence BE Study Dissolution	 Adequate Adequate	 3/7/2014 3/25/2014	 Q Liu P Jain
Toxicology/Clinical	N/A		
EA	Adequate, categorical exclusion per 21CFR 25.15 and 25.31(a)		MA Rahman
Radiopharmaceutical	N/A		
Samples requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturer of the DS, Omega-3 acids ethyl esters USP	(b) (4)		
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Contract Manufacturer of the DP, Omega-3 Acids Ethyl Esters soft gel Capsules,1 gm	*Emcure Pharmaceuticals USA Inc., 21 Cotters Ln ste B, East Brunswick, NJ*	3005139373	Acceptable as of 01/21/2014

Chemistry Review for ANDA 91018

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The drug product, Omega-3-Acid Ethyl Esters is a soft gelatin capsule containing 1 g fish oil and it is now official in the current USP monograph. The drug product is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia. The mechanism of action of Omega-3-acid ethyl esters is not completely understood. However, the potential mechanism of action include inhibition of acyl-CoA:1, 2-diacylglycerol acyltranferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. The proposed generic drug product is a softgel capsule containing at least 900 mg of Omega-3-acid ethyl esters, predominantly consisting of ethyl esters of eicosapentaenoic acid (EPA-465 mg) and docosahexaenoic acid (DHA-375 mg). The drug product also contains gelatin as a shell, glycerin [(b) (4)] [(b) (4)] as an imprinting. The drug product soft gelatin capsules are manufactured at Emcure Pharmaceuticals USA Inc. a contract DP manufacturer for the ANDA applicant, Par Pharmaceutical Inc.

The drug product, Omega-3-Acid Ethyl Esters Capsules, 1 gm contains polyunsaturated fatty acids [(b) (4)] The drug product is proposed to be stored in HDPE bottle with CRC closure which is similar with the RLD.

The drug product, Omega-3-Acid Ethyl Esters Capsules, 1 g is a soft gelatin capsule for oral administration which contain Omega-3-Acid Ethyl Esters, Gelatin NF, Glycerine, USP, Purified Water, USP, [(b) (4)] Shellac Glaze, Isopropyl Alcohol, Simethicone, Propylene Glycol, Titanium Dioxide, Ammonium Hydroxide, N-Butyl Alcohol. The soft gelatin capsules are manufactured by [(b) (4)]

Maximum daily dose is 4 g/day as per labeling insert information.

The drug product: based on the ICH Guideline Q3B (R2), reporting threshold (RT):

0.05%, Identification threshold (IT) for any unspecified impurity: 0.10%; Qualification threshold (QT) for any specified impurity: 0.15%.

Proposed expiry: Firm proposes an expiration period of 24 months for drug product based on 3 months accelerated stability data (40 ± 2 ^{0}C/75 ± 5% RH). Storage condition: Proposed generic label recommends storage at 25^{0}C (77^{0}F); excursions permitted to 15 ^{0} to 30 ^{0}C (59 ^{0} to 86 ^{0}F) [USP Controlled Room Temperature]. Do not freeze. Proposed Omega-3-acid ethyl esters capsules, 1 g are pale yellow, clear, oval soft-gelatin capsules imprinted "P019" in white ink. LOVAZA® (RLD) capsules are transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

Drug Substance:
The drug substance, Omega-3-acid ethyl esters (b) (4) is light yellow oil, free flowing. It is soluble in ethanol and acetone and not soluble in water. It is a fish oil fatty acid ester containing 465 mg EPA (eicosapentanoic acid ethyl ester) and 375mg DHA (docosahexaenoic acid ethyl ester), at least 900mg total Omega-3 as EE and 800-880mg of the sum of EPA and DHA. In addition, the drug substance is also consistent of mixture of the ethyl esters of five other omega-3 fatty acids per USP monograph and the proposed drug substance has no control over these fatty acids esters. It has also (b) (4) mg/g α-tocopherol as an antioxidant to protect from oxidation. Omega-3-acid ethyl esters (b) (4) are manufactured by (b) (4) The DMF (b) (4) referenced for the drug substance is currently inadequate.

Maximum daily dose is 4 g/day as per labeling insert information.
Impurity Threshold: The drug substance: based on the ICH Guideline Q3A (R2), reporting threshold (RT): 0.03%; Identification threshold (IT) for any unspecified impurity: 0.05%; Qualification threshold (QT) for any specified impurity: 0.05%.

B. Description of How the Drug Product is Intended to be Used

Omega-3-acids ethyl esters Capsules, to be taken as directed. The daily dose of Omega-3-acid ethyl esters capsule is 4 grams per day taken as a single 4 grams dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily). The patients are advised to shallow Omega-3-acid ethyl esters capsules whole and do not break open, crush, dissolve or chew. Patient should be on an appropriate lipid-lowering diet before receiving Omega-3-acid ethyl esters capsules. Proposed drug products will be available in 60's count and 120's count HDPE bottles and caps. See the drug product labeling for further information.

C. Basis for Approvability or Not-Approval Recommendation

The CMC review is currently acceptable per the review team recommendations. ANDA approvability is pending Division review and other disciplines. This CMC review may require an addendum based on recommendations made by other review disciplines.

GDEA Certification:

Debarment Certification:
Provided in section 1.3.3.
cGMP Statement:
Provided

Reprocessing Statement:
N/A

Letters of Authorization:
Provided in section 1.4.

Request for Bio-waiver:
N/A

Citizen Petition and/or Control Request Linked to the Application:
N/A

Environnemental Impact Considerations/Categorical Exclusions:
Claim of categorical exclusion is provided in section 1.12.14

III. List of Deficiencies To Be Communicated: (none)

ADMINISTRATIVE

Endorsement Block
Chemist Name/Date: M A Rahman, PhD/05/07/2014
Chemistry Team Leader Name/Date: Laxma R Nagavelli, PhD/5/29/2014
Division Director: Vilayat A Sayeed, PhD/5/30/2014
Project Manager Name: Leigh Ann Sears/5/30/2014

TYPE OF LETTER: CMC Acceptable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MD A RAHMAN
05/30/2014

STEVEN W YANG on behalf of LEIGH A SEARS
06/03/2014

LAXMA R NAGAVELLI
06/03/2014

VILAYAT A SAYEED
06/04/2014

CHEMISTRY REVIEW

First Generic: Yes
CMC: Not Acceptable-NA Minor
Labeling: Inadequate
EES: Acceptable
Bio: Adequate

ANDA 91018

Omega-3-acid ethyl esters capsules, 1 gm

PAR Pharmaceutical Inc.

M A Rahman
Team 34
Division of Chemistry III
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 91018

2. REVIEW #: R03

3. REVIEW DATE: 02/25/2014

4. REVIEWER: M A Rahman, PhD

5. PREVIOUS DOCUMENTS: N/A

Previous Document(s)	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original ANDA	November 10, 2008
Amendment	October 14, 2009
Amendment	February 12, 2010
Gratuitous Amendment	March 02, 2010
Amendment	September 28, 2011
Correspondence	March 17, 2011
Amendment	December 07, 2011
Correspondence	May 15, 2012
Patent amendment	May 18, 2012
Amendment	Nov 1, 2013 (Letter 10/31/2013)

7. NAME & ADDRESS OF APPLICANT:

Name:	Par Pharmaceutical Inc.
Address:	One Ram Ridge Road, Spring Valley, NY 10977
Representative:	Janis Picurro, Director, Regulatory Affairs
Telephone:	845-425-7100
Fax:	845-573-5795

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Omega-3-Acid Ethyl Esters Capsules, 1 gm

9. LEGAL BASIS FOR SUBMISSION:

This ANDA # 91018 of Omega-3-Acid Ethyl Esters Capsules, 1 gm is being submitted based on the reference listed drug (RLD): Lovaza® Capsules (Omega-3-Acid Ethyl Esters Capsules, 1 gm) is approved for GlaxoSmithKline (NDA 21654).

The following United States Patents is/are listed in "Electronic Orange Book" (*Approved Drug Products with Therapeutic Equivalence Evaluations* for the above-identified RLD:

1.3.5.1.-1 Patents Listed for the Reference Listed Drug			
Application Number	**Patent Number**	**Patent Expiration**	**Use Code**
021654	5502077	March 26, 2013	U-822
021654	5656667	August 27, 2018	U-822
021654	5698594	August 4, 2009	U-822

Par submits the following certifications to these patents:

The below table lists all certifications provided herein, addressing Section 505(j)(2)(A) of the FD&C Act. Certifications outlined in the table below are provided on the following pages.

Table 1.3.5.2-1 List of Applicable Certifications		
Patent Number	**Certification**	**Expiration (PED*, if applic.)**
5502077	Paragraph IV	March 26, 2013
5656667	Paragraph IV	August 27, 2018
5698594	Paragraph IV	August 4, 2009

*PED – patent expiration extended due to pediatric exclusivity (only if applicable)

Please refer to Section 1.12.11 for the relevant "Electronic Orange Book" pages.

Pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, Par Pharmaceutical Inc. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 7,732,488 is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of 1 g capsules of omega-3-acid ethyl esters, for which this application is submitted. Par Pharmaceutical Inc. previously submitted certifications pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act with respect to U.S. Patent No. 5,502,077 and U.S. Patent No. 5,656,667. Par Pharmaceutical Inc. does not amend, withdraw, or alter those previously submitted certifications.

10. PHARMACOL. CATEGORY: Triglyceride reducing agent

11. DOSAGE FORM: Capsules (Soft Gelatin)

12. STRENGTH/POTENCY: 1 gm (MDD = 4 gm)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X___Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__X__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Omega-3 acid ethyl esters (b) (4) is a fish-oil fatty acid ester concentrate containing the followings:

Chemical Name for EPA:

• Eicosapentaenoic acid

Chemical Name for DHA:

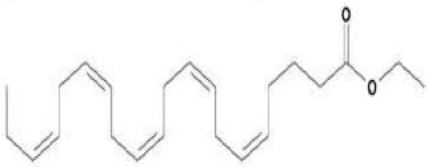
Docosahexaenoic acid

CAS #: 91051-05-7

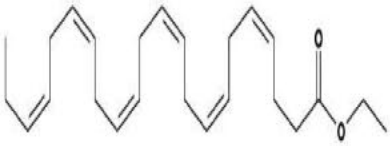
United States Adopted Name (USAN): Omega-3-Acid Ethyl Esters

International Non-Proprietary Name (INN): Omega-3-Acid Ethyl Esters (b) (4)

Structure for EPA-EE (Eicosapentaenoic Acid Ethyl Ester):



Structure for DHA-EE (Docosahexaenoic acid Ethyl Ester):



Molecular Formula:

• EPA-EE – $C_{22}H_{34}O_2$

• DHA-EE – $C_{24}H_{36}O_2$

Molecular Weight:

• EPA-EE – 330.51

• DHA-EE – 356.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	03/26/2014	Reviewed by MA Rahman
	III			3			
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* number to be assigned

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	01/21/2014	Reviewed by T. Sharp
Methods Validation	N/A		
Labeling	Inadequate	2/27/2014	Reviewed by B. Turner
Bioequivalence BE Study Dissolution	 Adequate Adequate	 3/7/2014 3/25/2014	 Reviewed by Q Liu Reviewed by P Jain
Toxicology/Clinical	N/A		
EA	Adequate, categorical exclusion per 21CFR 25.15 and 25.31(a)		Reviewed by MA Rahman
Radiopharmaceutical	N/A		
Samples requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturer of the DS, Omega-3 acids ethyl esters (b) (4)	(b) (4)		
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Contract Manufacturer of the DP, Omega-3 Acids Ethyl Esters soft gel Capsules,1 gm	*Emcure Pharmaceuticals USA Inc., 21 Cotters Ln ste B, East Brunswick, NJ*	3005139373	Acceptable as of 01/21/2014

Following this page, 2 Pages Withheld in Full as (b)(4)

Chemistry Review for ANDA 91018

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable, NA-Minor

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The drug product, Omega-3-Acid Ethyl Esters is a soft gelatin capsule containing 1 g fish oil and it is now official in the current USP monograph. The drug product is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia. The mechanism of action of Omega-3-acid ethyl esters is not completely understood. However, the potential mechanism of action include inhibition of acyl-CoA:1, 2-diacylglycerol acyltranferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. The proposed generic drug product is a softgel capsule containing at least 900 mg of Omega-3-acid ethyl esters, predominantly consisting of ethyl esters of eicosapentaenoic acid (EPA-465 mg) and docosahexaenoic acid (DHA-375 mg). The drug product also contains gelatin as a shell, glycerin (b) (4) (b) (4) as an imprinting. The drug product soft gelatin capsules are manufactured at Emcure Pharmaceuticals USA Inc. a contract DP manufacturer for the ANDA applicant, Par Pharmaceutical Inc.

The drug product, Omega-3-Acid Ethyl Esters Capsules, 1 gm contains polyunsaturated fatty acids (b) (4) . The drug product is proposed to be stored in HDPE bottle with CRC closure which is similar with the RLD.

The drug product, Omega-3-Acid Ethyl Esters Capsules, 1 g is a soft gelatin capsule for oral administration which contain Omega-3-Acid Ethyl Esters, Gelatin NF, Glycerine, USP, Purified Water, USP, (b) (4) Shellac Glaze, Isopropyl Alcohol, Simethicone, Propylene Glycol, Titanium Dioxide, Ammonium Hydroxide, N-Butyl Alcohol. The soft gelatin capsules are manufactured by (b) (4)

Maximum daily dose is 4 g/day as per labeling insert information.

The drug product: based on the ICH Guideline Q3B (R2), reporting threshold (RT):

0.05%, Identification threshold (IT) for any unspecified impurity: 0.10%; Qualification threshold (QT) for any specified impurity: 0.15%.

Proposed expiry: Firm proposes an expiration period of 24 months for drug product based on 3 months accelerated stability data (40 ± 2 ^{0}C/75 ± 5% RH). Storage condition: Proposed generic label recommends storage at 25^{0}C (77^{0}F); excursions permitted to 15 ^{0} to 30 ^{0}C (59 ^{0} to 86 ^{0}F) [USP Controlled Room Temperature]. Do not freeze. Proposed Omega-3-acid ethyl esters capsules, 1 g are pale yellow, clear, oval soft-gelatin capsules imprinted "P019" in white ink. LOVAZA® (RLD) capsules are transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

Drug Substance:
The drug substance, Omega-3-acid ethyl esters (b)(4) is light yellow oil, free flowing. It is soluble in ethanol and acetone and not soluble in water. It is a fish oil fatty acid ester containing 465 mg EPA (eicosapentanoic acid ethyl ester) and 375mg DHA (docosahexaenoic acid ethyl ester), at least 900mg total Omega-3 as EE and 800-880mg of the sum of EPA and DHA. In addition, the drug substance is also consistent of mixture of the ethyl esters of five other omega-3 fatty acids per USP monograph and the proposed drug substance has no control over these fatty acids esters. It has also (b)(4) mg/g α-tocopherol as an antioxidant to protect from oxidation. Omega-3-acid ethyl esters (b)(4) are manufactured by (b)(4) The DMF (b)(4) referenced for the drug substance is currently inadequate.

Maximum daily dose is 4 g/day as per labeling insert information.
Impurity Threshold: The drug substance: based on the ICH Guideline Q3A (R2), reporting threshold (RT): 0.03%; Identification threshold (IT) for any unspecified impurity: 0.05%; Qualification threshold (QT) for any specified impurity: 0.05%.

B. Description of How the Drug Product is Intended to be Used

Omega-3-acids ethyl esters Capsules, to be taken as directed. The daily dose of Omega-3-acid ethyl esters capsule is 4 grams per day taken as a single 4 grams dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily). The patients are advised to shallow Omega-3-acid ethyl esters capsules whole and do not break open, crush, dissolve or chew. Patient should be on an appropriate lipid-lowering diet before receiving Omega-3-acid ethyl esters capsules. Proposed drug products will be available in 60's count and 120's count HDPE bottles and caps. See the drug product labeling for further information.

C. Basis for Approvability or Not-Approval Recommendation

The application is Not Approval due to minor CMC deficiencies.

Following this page, 68 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

A **APPENDICES**

A.1 ***Facilities and Equipment (biotech only)***

A.2 ***Adventitious Agents Safety Evaluation***

A.3 ***Novel Excipients***

A.4 ***Nanotechnology Product Information***

R **REGIONAL INFORMATION**

R.1 ***Executed Batch Records***

Executed BRs for manufacturing and packaging of drug substance and drug product have been provided by the firm.

R.2 ***Comparability Protocols***

N/A

R.3 ***Methods Validation Package***

MV package provided by the firm.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification:
Provided in section 1.3.5
Exclusivity:
Provided in section 1.3.5

GDEA Certification:

Debarment Certification:
Provided in section 1.3.3.
cGMP Statement:
Provided

Reprocessing Statement:
N/A

Letters of Authorization:

Provided in section 1.4.

Request for Bio-waiver:
N/A

Citizen Petition and/or Control Request Linked to the Application:
N/A

Environnemental Impact Considerations/Categorical Exclusions:
Claim of categorical exclusion is provided in section 1.12.14

III. List of Deficiencies To Be Communicated: (see next page)

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91018 **APPLICANT: Par Pharmaceutical, Inc.**

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules USP, 1 gm

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies

1. The drug master file # (b) (4) for Omega-3 acid ethyl esters is currently inadequate. The DMF holder, (b) (4) has been notified. Please do not respond to this letter until the DMF holder has informed you that they have responded to all the deficiencies. Please update your drug substance specifications in consultation with your DMF holder and provide updated methods and validations as applicable.

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your proposed (b) (4) of this review. Please acknowledge.

2. Please make all applicable changes to your drug product release/stability specifications per the Division of Bioequivalence recommendations.

Sincerely yours,
{See appended electronic signature}
Vilayat A Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

ADMINISTRATIVE

Endorsement Block
Chemist Name/Date: M A Rahman, PhD/02/27/2014; 3/12/2014
Chemistry Team Leader Name/Date: Laxma R Nagavelli, PhD/3/4/2014; 3/14/2014
Division Director: Vilayat A Sayeed, PhD/3/14/2014
Project Manager Name: Leigh Ann Sears/3/18/2014

TYPE OF LETTER: **NA Minor**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MD A RAHMAN
03/26/2014

STEVEN W YANG on behalf of LEIGH A SEARS
03/26/2014

LAXMA R NAGAVELLI
03/26/2014

VILAYAT A SAYEED
03/26/2014

First Generic
Not Approvable-Minor

ANDA 91018

Omega-3-acid ethyl esters capsules, 1 gm

PAR Pharmaceutical Inc.

M A Rahman
Team 34
Division of Chemistry III
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #: 91018**

2. **REVIEW #: R02**

3. **REVIEW DATE: 07/22/2013**

4. **REVIEWER: M A Rahman, PhD**

5. **PREVIOUS DOCUMENTS: N/A**

Previous Document(s)	Document Date

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original ANDA	November 10, 2008
Amendment	October 14, 2009
Amendment	February 12, 2010
Gratuitous Amendment	March 02, 2010
Amendment	September 28, 2011
Correspondence	March 17, 2011
Amendment	December 07, 2011

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Par Pharmaceutical Inc.
Address:	One Ram Ridge Road, Spring Valley, NY 10977
Representative:	Janis Picurro, Director, Regulatory Affairs
Telephone:	845-425-7100
Fax:	845-573-5795

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: N/A
Non-Proprietary Name (USAN): Omega-3-Acid Ethyl Esters Capsules, 1 gm

9. **LEGAL BASIS FOR SUBMISSION:**

This ANDA # 91018 of Omega-3-Acid Ethyl Esters Capsules, 1 gm is being submitted based on the reference listed drug (RLD): Lovaza® Capsules (Omega-3-Acid Ethyl Esters Capsules, 1 gm) is approved for GlaxoSmithKline (NDA 21654).

The following United States Patents is/are listed in "Electronic Orange Book" (*Approved Drug Products with Therapeutic Equivalence Evaluations* for the above-identified RLD:

1.3.5.1.-1 Patents Listed for the Reference Listed Drug			
Application Number	**Patent Number**	**Patent Expiration**	**Use Code**
021654	5502077	March 26, 2013	U-822
021654	5656667	August 27, 2018	U-822
021654	5698594	August 4, 2009	U-822

Par submits the following certifications to these patents:

The below table lists all certifications provided herein, addressing Section 505(j)(2)(A) of the FD&C Act. Certifications outlined in the table below are provided on the following pages.

Table 1.3.5.2-1 List of Applicable Certifications		
Patent Number	**Certification**	**Expiration (PED*, if applic.)**
5502077	Paragraph IV	March 26, 2013
5656667	Paragraph IV	August 27, 2018
5698594	Paragraph IV	August 4, 2009

*PED – patent expiration extended due to pediatric exclusivity (only if applicable)

Please refer to Section 1.12.11 for the relevant "Electronic Orange Book" pages.

Pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, Par Pharmaceutical Inc. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 7,732,488 is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of 1 g capsules of omega-3-acid ethyl esters, for which this application is submitted. Par Pharmaceutical Inc. previously submitted certifications pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act with respect to U.S. Patent No. 5,502,077 and U.S. Patent No. 5,656,667. Par Pharmaceutical Inc. does not amend, withdraw, or alter those previously submitted certifications.

10. PHARMACOL. CATEGORY: Triglyceride reducing agent

11. DOSAGE FORM: Capsules (Soft Gelatin)

12. STRENGTH/POTENCY: 1 gm (MDD = 4 gm)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X___**Rx** ___**OTC**

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

___X___Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Omega-3 acid ethyl esters (b) (4) is a fish-oil fatty acid ester concentrate containing the followings:

Chemical Name for EPA:

• Eicosapentaenoic acid

Chemical Name for DHA:

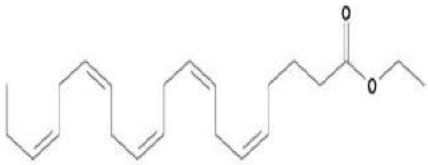
Docosahexaenoic acid

CAS #: 91051-05-7

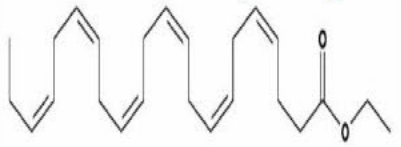
United States Adopted Name (USAN): Omega-3-Acid Ethyl Esters

International Non-Proprietary Name (INN): Omega-3-Acid Ethyl Esters (b) (4)

Structure for EPA-EE (Eicosapentaenoic Acid Ethyl Ester):



Structure for DHA-EE (Docosahexaenoic acid Ethyl Ester):



Molecular Formula:

• EPA-EE – $C_{22}H_{34}O_2$

• DHA-EE – $C_{24}H_{36}O_2$

Molecular Weight:

• EPA-EE – 330.51

• DHA-EE – 356.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Inadequate	08/21/2013	Reviewed by MA Rahman
	III			3			
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

* number to be assigned

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

APPEARS THIS WAY ON ORIGINAL

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	03/22/2011	Reviewed by De Smith
Methods Validation			
Labeling	Inadequate	11/18/2009	Reviewed by T. Vu
Bioequivalence BE Study Dissolution	 ECD Inadequate	 6/12/2013 8/11/2010	 Chang, Sherry Reviewed by Ke Ren
Toxicology/Clinical	N/A		
EA	Adequate, categorical exclusion per 21CFR 25.15 and 25.31(a)		Reviewed by MA Rahman
Radiopharmaceutical	N/A		
Samples requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturer of the DS, Omega-3 acids ethyl esters (b) (4)	(b) (4)		
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Contract Manufacturer of the DP, Omega-3 Acids Ethyl Esters soft gel Capsules,1 gm	*Emcure Pharmaceuticals USA Inc., 21 Cotters Ln ste B, East Brunswick, NJ*	3005139373	Acceptable as of 04/22/2011

Following this page, 2 Pages Withheld in Full as (b)(4)

Chemistry Review for ANDA 202299

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable, NA-Minor

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The drug product, Omega-3-Acid Ethyl Esters is a soft gelatin capsule containing 1 g fish oil and it is now official in the current USP monograph. The drug product is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia. The mechanism of action of Omega-3-acid ethyl esters is not completely understood. However, the potential mechanism of action include inhibition of acyl-CoA:1, 2-diacylglycerol acyltranferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. The proposed generic drug product is a softgel capsule containing at least 900 mg of Omega-3-acid ethyl esters, predominantly consisting of ethyl esters of eicosapentaenoic acid (EPA-465 mg) and docosahexaenoic acid (DHA-375 mg). The drug product also contains gelatin as a shell, glycerin (b) (4) (b) (4) as an imprinting. The drug product soft gelatin capsules are manufactured at Emcure Pharmaceuticals USA Inc. a contract DP manufacturer for the ANDA applicant, Par Pharmaceutical Inc.

The drug product, Omega-3-Acid Ethyl Esters Capsules, 1 gm contains polyunsaturated fatty acids (b) (4) The drug product is proposed to be stored in HDPE bottle with CRC closure which is similar with the RLD.

The drug product, Omega-3-Acid Ethyl Esters Capsules, 1 g is a soft gelatin capsule for oral administration which contain Omega-3-Acid Ethyl Esters, Gelatin NF, Glycerine, USP, Purified Water, USP, (b) (4) Shellac Glaze, Isopropyl Alcohol, Simethicone, Propylene Glycol, Titanium Dioxide, Ammonium Hydroxide, N-Butyl Alcohol. The soft gelatin capsules are manufactured by (b) (4)

Maximum daily dose is 4 g/day as per labeling insert information.

The drug product: based on the ICH Guideline Q3B (R2), reporting threshold (RT):

0.05%, Identification threshold (IT) for any unspecified impurity: 0.10%; Qualification threshold (QT) for any specified impurity: 0.15%.

Proposed expiry: Firm proposes an expiration period of 24 months for drug product based on 3 months accelerated stability data (40 ± 2 ^{0}C/75 ± 5% RH). Storage condition: Proposed generic label recommends storage at 25^{0}C (77^{0}F); excursions permitted to 15 ^{0} to 30 ^{0}C (59 ^{0} to 86 ^{0}F) [USP Controlled Room Temperature]. Do not freeze. Proposed Omega-3-acid ethyl esters capsules, 1 g are pale yellow, clear, oval soft-gelatin capsules imprinted "P019" in white ink. LOVAZA® (RLD) capsules are transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation LOVAZA.

Drug Substance:
The drug substance, Omega-3-acid ethyl esters (b)(4) is light yellow oil, free flowing. It is soluble in ethanol and acetone and not soluble in water. It is a fish oil fatty acid ester containing 465 mg EPA (eicosapentanoic acid ethyl ester) and 375mg DHA (docosahexaenoic acid ethyl ester), at least 900mg total Omega-3 as EE and 800-880mg of the sum of EPA and DHA. In addition, the drug substance is also consistent of mixture of the ethyl esters of five other omega-3 fatty acids per USP monograph and the proposed drug substance has no control over these fatty acids esters. It has also (b)(4) mg/g α-tocopherol as an antioxidant to protect from oxidation. Omega-3-acid ethyl esters (b)(4) are manufactured by (b) (4) The DMF (b) (4) referenced for the drug substance is currently inadequate.

Maximum daily dose is 4 g/day as per labeling insert information.
Impurity Threshold: The drug substance: based on the ICH Guideline Q3A (R2), reporting threshold (RT): 0.03%; Identification threshold (IT) for any unspecified impurity: 0.05%; Qualification threshold (QT) for any specified impurity: 0.05%.

B. Description of How the Drug Product is Intended to be Used

Omega-3-acids ethyl esters Capsules, to be taken as directed. The daily dose of Omega-3-acid ethyl esters capsule is 4 grams per day taken as a single 4 grams dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily). The patients are advised to shallow Omega-3-acid ethyl esters capsules whole and do not break open, crush, dissolve or chew. Patient should be on an appropriate lipid-lowering diet before receiving Omega-3-acid ethyl esters capsules. Proposed drug products will be available in 60's count and 120's count HDPE bottles and caps. See the drug product labeling for further information.

C. Basis for Approvability or Not-Approval Recommendation

The application is Not Approval due to minor CMC deficiencies.

Following this page, 58 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

A **APPENDICES**

A.1 ***Facilities and Equipment (biotech only)***

A.2 ***Adventitious Agents Safety Evaluation***

A.3 ***Novel Excipients***

A.4 ***Nanotechnology Product Information***

R **REGIONAL INFORMATION**

R.1 ***Executed Batch Records***

Executed BRs for manufacturing and packaging of drug substance and drug product have been provided by the firm.

R.2 ***Comparability Protocols***

N/A

R.3 ***Methods Validation Package***

MV package provided by the firm.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification:
Provided in section 1.3.5
Exclusivity:
Provided in section 1.3.5

GDEA Certification:

Debarment Certification:
Provided in section 1.3.3.
cGMP Statement:
Provided

Reprocessing Statement:
N/A

Letters of Authorization:

Provided in section 1.4.

Request for Bio-waiver:
N/A

Citizen Petition and/or Control Request Linked to the Application:
N/A

Environnemental Impact Considerations/Categorical Exclusions:
Claim of categorical exclusion is provided in section 1.12.14

III. List of Deficiencies To Be Communicated (see next page):

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91018 **APPLICANT: Par Pharmaceutical, Inc.**

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules USP, 1 gm

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies

1. The drug master file # (b) (4) for Omega-3 acid ethyl esters is currently inadequate. The DMF holder, (b) (4) has been notified. Please do not respond to this letter until the DMF holder has informed you that they have responded to all the deficiencies. Please update your drug substance specifications in consultation with your DMF holder and provide updated methods and validations as applicable.

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your proposed (b) (4) of this review. Please acknowledge.

2. Please make all applicable changes to your drug product release/stability specifications per the Division of Bioequivalence recommendations.

3. Please update the drug product name and other relevant information to comply with the current USP monograph for the drug product.

4. (b) (4)

Sincerely yours,

{See appended electronic signature}

Vilayat A Sayeed, Ph.D
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

ADMINISTRATIVE

Endorsement Block
Chemist Name/Date: M A Rahman, PhD/07/31/2013; 8/18/2013
Chemistry Team Leader Name/Date: Laxma R Nagavelli, PhD/8/15/2013; 8/19/2013
Division Director: Vilayat A Sayeed, PhD/ 8/21/2013
Project Manager Name: Leigh Ann Sears/8/21/2013

TYPE OF LETTER: NA Minor

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MD A RAHMAN
08/21/2013

LEIGH A SEARS
08/21/2013

LAXMA R NAGAVELLI
08/21/2013

VILAYAT A SAYEED
08/21/2013

ANDA 091018

Omega-3-Acid Ethyl Esters Capsules, 1 g

Par Pharmaceutical, Inc.

Haitao Li
Office of Generic Drugs
Division of Chemistry III
Team 34

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 091018

2. REVIEW #: 1

3. REVIEW DATE: 6/7/11

4. REVIEWER: Haitao Li, Ph.D

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission Reviewed	Document Date
Original	November 10, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Par Pharmaceutical, Inc.
Address:	One Ram Ridge Road Spring Valley, New York 10977
Representative:	Karen Rocco
Telephone: Fax:	(845) 425-7100 845-639-5201

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Omega-3-Acid Ethyl Esters Capsules

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug: Lovaza™ Capsules
RLD Company SmithKline Beecham, NDA # 021654

The firm also provided Paragraph IV certification.

10. PHARMACOLOGICAL CATEGORY: indicated as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients.

11. DOSAGE FORM: Soft gelatin capsules

12. STRENGTH/POTENCY: 1g

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

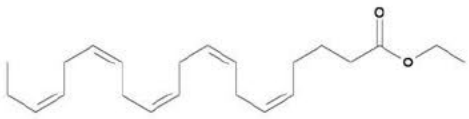
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

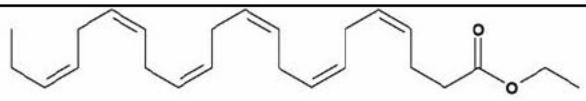
_____SPOTS product – Form Completed
__X__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING

_____Nano product – Form Completed
__X__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature, Molecular Structure, Molecular Formula, and Molecular Weight	
Recommended International Nonproprietary Name (INN):	omega-3-acid ethyl esters (b) (4)
Compendial name, if relevant:	omega-3-acid ethyl esters (European Pharmacopeia)
Chemical name(s):	a combination of ethyl esters of eicosapentaenoic acid (EPA – approximately 465 mg) and docosahexaenoic acid (DHA – approximately 375 mg)
Company or laboratory code:	(b) (4)
Other non-proprietary name(s), e.g. USAN, JAN, BAN:	omega-3-acid ethyl esters
Chemical Abstracts Service (CAS) registry number:	CAS No: 91051-05-7
Molecular Structure	
Molecular Formula and Molecular Weight	The structural formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.

Molecular Structure	
Molecular Formula and Molecular Weight	The structural formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.

Background:

Lovaza (Omega-3-acid ethyl esters) soft gelatin capsules was approved on November 10, 2004, as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia.

The USP 34 for Omega-3 Acid Ethyl Esters defines the drug substance to contain 7 omega-3 acid ethyl esters. The Agency considers that a pharmaceutically equivalent API contains two quantitatively major components, EPA EE and DHA EE, in the ranges specified in the USP. Quantitative ranges are not specified for three additional omega-3 acid EEs present greater than 1% w/w in the RLD, Lovaza (GSK). These three compounds are SDA EE, HPA EE, and DPA EE.

Pursuant to CMC request, the firm provided quantitative levels of the seven omega-3 acid EEs in multiple batches of the RLD and one batch of the test product. The firm has not provided comparable results for the quantitation of components using in-house analytical method against the USP recommended method. For setting the quantitative ranges of the components for the proposed drug product, the firm needs to provide data for six batches RLD using the official (USP) analytical method.

Reviewer's comment:

The firm is requested to provide responses to the following listed deficiencies (see letter) prior to full CMC review of the application.

III. List of Deficiencies to be communicated:

ANDA: 091018
APPLICANT: Par Pharmaceutical, Inc.
DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules

The deficiencies presented below represent a Minor deficiency.

A. Deficiencies:

(b) (4)

Upon receiving the above requested data a complete CMC review of the application will be undertaken.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:

HFD-630/ H. Li, Review Chemist/6/7/2011
HFD-630/ L. Nagavelli, Team Leader / 6/7/2011
HFD-617/L. Sears, PM/ 6/07/2011

V:\Chemistry Division III\Team 12\Final Version For DFS Folder\ANDA\91018R01.doc

TYPE OF LETTER: NOT APPROVABLE – NA-Minor

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAITAO LI
06/07/2011

LEIGH A SEARS
06/07/2011

LAXMA R NAGAVELLI
06/07/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91018

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE
DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	091018
Drug Product Name	Omega-3 Acid Ethyl Esters Capsules
Strength (s)	1 gram
Applicant Name	Par Pharmaceutical Inc.
Applicant Address	One Ram Ridge Road Spring Valley, New York 10977
US Agent Name and the mailing address	Julia Szozda
US Agent's Telephone Number	845-573-5780
US Agent's Fax Number	845-573-5795
Original Submission Date(s)	11/10/2008
Submission Date(s) of Amendment(s) Under Review	3/14/2014 (Dissolution Acknowledgement)
First Generic	No
Reviewer	Priti Jain
OVERALL DISSOLUTION REVIEW RESULT	**ADEQUATE**

EXECUTIVE SUMMARY

This is a review of the dissolution method and/or specification acknowledgement from Par Pharmaceutical Inc. Par Pharmaceutical Inc. has accepted the following FDA-recommended dissolution method and specifications.

RECOMMENDATIONS

From a bioequivalence point of view, Par Pharmaceutical Inc. has met the requirements for in vitro dissolution testing. The dissolution testing section of the application is adequate and we have no further questions at this time.

Medium	4.0% Triton X-100 in 0.01 N HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)

DISSOLUTION COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 091018

APPLICANT: Par Pharmaceuticals Inc.

DRUG PRODUCT: Omega-3 Acid Ethyl Esters Capsules, 1 gram

The Division of Bioequivalence I (DB1) has completed its review of your submissions acknowledged on the coversheet and has no further questions at this time. We acknowledge that you will conduct the dissolution testing of your test product using the following FDA-recommended dissolution method and specifications:

Medium	4.0% Triton X-100 in 0.01 N HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)

Also, as mentioned in your submission, DB1 acknowledges that you will have an effective finished product/stability monograph in place prior to conducting the QCRT.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

I. *Completed Assignment for 091018 ID: 22103*

Reviewer: Jain, Priti

Date Completed:

Verifier: Solana-Sodeinde, Diana

Date Verified:

Division: Division of Bioequivalence

Description: Dissolution Acknowledgement Review for ANDA 91018

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
22103	3/20/2014	Dissolution Data (REGULAR)	Dissolution Acknowledgement	1	1	Edit	Delete
				Total:	1		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRITI R JAIN
03/24/2014

DIANA A SOLANA-SODEINDE on behalf of DALE P CONNER
03/25/2014

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091018			
Drug Product Name	Omega-3 Acid Ethyl Esters Capsules			
Strength(s)	1 g			
Applicant Name	Par Pharmaceutical Inc.			
Address	One Ram Ridge Road Spring Valley, New York 10977			
Applicant's Point of Contact	Julie Szozda, Submissions Manager, Regulatory Affairs			
Contact's Telephone Number	845- 573- 5780			
Contact's Fax Number	845- 573- 5795			
Original and Amendment Submission Date(s)	November 10, 2008 September 30, 2009 (dissolution amendment) May 05, 2010 (dissolution amendment) August 26, 2010 (QCRT specifications acknowledgement)			
Submission Dates of Amendments Under Review	December 07, 2011 (Submission of additional Fed Study 2011-2545) June 25, 2013 (Components of firm's test product) November 01, 2013 (reformulation and *in vitro* testing results) February 18, 2014 (response to ECD letter) February 27, 2014 (response to ECD letter)			
Reviewer	Qing Liu, Ph.D.			
Study Number (s)	2008-1806	2008-1807	2008-1835	2011-2545
Study Type (s)	Fasting (single-dose study, RLD product only)	Fed (single-dose study, RLD product only)	Fed (single-dose, two-way crossover study using test and RLD product)	Fed (single dose 4-way fully replicated reference-scaled crossover study using test and RLD product)
Strength (s)	4 x 1 g	4 x 1 g	4 x 1 g	4 x 1 g
Clinical Site	Pharma Medica Research Inc.			
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6			
Analytical Site	(b) (4)			
Analytical Site Address				
Overall Review Result	**ADEQUATE (BE Review Only)**			
OSI	**N/A**			

Bioequivalence Study Tracking/supporting Document#	**Study / Test Type**	**Strength**	**Review Result**
1,7,12,16, 26,27,29	In Vitro Capsule Quantitative Rupture Test	1 gram	ADEQUATE (for BE review)

1	Fasting (Pilot Study)	1 gram	INADEQUATE (for information only)
1	Fed (Pilot Study)	1 gram	INADEQUATE (for information only)
1	Fed BE Study (failed pivotal study)	1 gram	INADEQUATE (for information only)
21,25	Fed BE Study (passing pivotal study)	1 gram	INADEQUATE (for information only)

1 EXECUTIVE SUMMARY

This application is referencing NDA 021654 for Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1 g, from GlaxoSmithKline.

Although the current ANDA contains several *in vivo* bioequivalence (BE) studies and *in vitro* quantitative capsule rupture (QCRT) studies, using several different drug release methods, the ANDA is considered qualified for the *in vitro* QCRT BE testing option, based on the test formulation submitted in the amendment dated November 1, 2013. The review of *in vivo* BE studies is for information only.

The firm submitted QCRT data, using both basket and flow-through cell. Based on the data submitted, QCRT testing with basket method was recommended to the firm as regulatory method for release and stability testing of the test product (DARRTS, ANDA 091018: REV-BIOEQ-02(Dissolution Review) dated 03/06/2014). The QCRT is currently inadequate, with respect to regulatory drug release testing, pending firm's acknowledgement of FDA-recommended specifications. The QCRT testing data from the test and reference products are comparable (F2>50) with both methods, thus demonstrating in vitro drug release equivalence. For the purpose of waiver of additional acceptable *in vivo* BE studies, the QCRT testing data are **adequate**. The firm's *in vivo* study waiver is granted.

The BE testing portion of the ANDA is **adequate**.

2 TABLE OF CONTENTS

3 SUMMARY OF STUDY SUBMISSION HISTORY

As per the Draft Guidance for Omega-3-Acid Ethyl Esters posted on September 2012[1], there are two options to establish BE of this drug product: *In Vitro* or *In Vivo* Studies. The firm's submission history of *in vivo* studies, and *in vitro* studies (formulation and quantitative capsule rupture test (QCRT)) are summarized as follows:

***In Vivo* Studies:**

On November 10, 2008 (prior to the publication of FDA Draft Guidance for Omega-3-Acid Ethyl Esters) , Par Pharmaceuticals submitted 02 pilot studies **on RLD only** and 01 **pivotal fed** bioequivalence (BE) study in support of its application:

1. A single dose pharmacokinetic study of the Reference Listed Drug (RLD) product Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1 g, **fasting** study 2008-1806.
2. A single dose pharmacokinetic study of the RLD product, Lovaza (Omega-3-Acid Ethyl Esters) capsules, 1g, **fed** study 2008-1807.
3. A single dose two way crossover study comparing its test product, Omega-3 Acid Ethyl Esters Capsules, 1 g to the RLD product, Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1 g under **fed** BE study 2008-1835

The firm provided the pharmacokinetic results (AUCt and Cmax) and statistical results for these three studies.

For the pivotal fed BE study 2008-1835, the Cmax parameter for the free fatty acids for Eicosapentaenoic Acid (EPA) was not within the 90% CI acceptance criteria of 80-125%, i.e. 109.14-**130.04%.**

On December 07, 2011 (prior to the publication of FDA Draft Guidance for Omega-3-Acid Ethyl Esters), the firm submitted another **pivotal fed BE** study:

4. A single dose 4-way fully replicated reference scaled crossover design comparing its test product, Omega-3 Acid Ethyl Esters Capsules, 1 g to the RLD product, Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1 g under **fed** BE study 2011-2545. The firm's results of this pivotal fed BE study are summarized in the tables below:

[1] Draft Guidance: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf.

Fed Bioequivalence Study (2011-2545)

Fed Bioequivalence Study (2011-2545)						
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Eicosapentaenoic Acid from Total Lipids						
Parameter	***Test***	***Ref***	***Ratio (%)***	***90% C.I.***	***Intra-Sub Within Ref SD (s_{WR})***	***95% Upper Bound for RSABE Criterion***
Cmax	47.61	48.04	99.09	93.45-105.08	0.197	N/A
AUC0-72	N/A	N/A	98.37	N/A	0.378	-0.081717
Docosahexaenoic Acid from Total Lipids						
Parameter	***Test***	***Ref***	***Ratio (%)***	***90% C.I.***	***Intra-Sub Within Ref SD (s_{WR})***	***95% Upper Bound for RSABE Criterion***
Cmax	29.54	29.14	101.37	93.99-109.33	0.231	N/A
AUC0-72	N/A	N/A	103.08	N/A	0.339	-0.060883

Fed Bioequivalence Study (2011-2545)				
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Eicosapentaenoic Acid from Free Fatty Acids				
Parameter	***Test***	***Ref***	***Ratio (%)***	***90% C.I.***
Cmax	568.1	585.0	97.12	90.70-103.99
AUC0-72	5320.1	5227.7	101.77	95.93-107.96

Docosahexaenoic Acid from Free Fatty Acids						
Parameter	***Test***	***Ref***	***Ratio (%)***	***90% C.I.***	***Intra-Sub Within Ref SD (s_{WR})***	***95% Upper Bound for RSABE Criterion***
Cmax	N/A	N/A	95.79	N/A	0.313	-0.051539
AUC0-72	N/A	N/A	101.71	N/A	0.298	-0.048937

The reviewer has conducted a brief evaluation of the *in vivo* data submitted by the firm[2]. The firm's Fed Bioequivalence Study (2011-2545) is **inadequate**. The firm did not measure the analytes recommended in the current draft guidance for Omega-3-Acid Ethyl Esters Capsules[1]. In addition, the firm did not provide data on a fasting BE study (per the Guidance, a fasting BE study is recommended). The "*In Vivo* Studies" of the application is **inadequate.**

Nevertheless, at the time of the current review, the firm has opted to pursue the *in vitro* study option (refer to discussion below), therefore the review of the *in vivo* data is for information only.

[2] Since the firm has expressed its intention to opt "In Vitro Study" for its application (see the in vitro study section for details), the in vivo BE studies in this report were evaluated only for the completeness of the review process

An inspection was requested for the clinical site Pharma Medica Research, Inc., 4770 Sheppard Avenue East, Toronto, Ontario, Canada M1S 3V6 under ANDA (b) (4). The inspection is pending. **However, since the firm opt to follow the "*in vitro* option", the inspection for the clinical site of the *in vivo* study is not necessary.**

***In Vitro* Study:**

For this option, the Draft Guidance on Omega-3-Acid Ethyl Esters states "*Providing the recommendations on active pharmaceutical ingredient (API) in Appendix 1 and the recommendations on antioxidant in Appendix 2 are both met, the capsule fills of the Test and Reference drug products are considered very similar, and BE may be established based solely on an in vitro method (Quantitative Capsule Rupture Test…) that assures equivalent release of API from the capsules."*

1. On November 10, 2008 and December 07, 2011,the firm submitted its formulation for its Omega-3 Acid Ethyl Esters Capsules, 1 g, (Lot No.: 21680902 used in its first pivotal fed BE study #2008-1835 and Omega-3 Acid Ethyl Esters Capsules, 1 g, Lot No. E03110201 used in its second pivotal study fed BE study # 2011-2545).

2. On 06/12/2013, DBI sent the firm a letter [3], asking about the breakdown details of the formulation of the firm's test product. On 06/25/2013, in response to DBI's request, the firm provided breakdown formulations of two lots of test products (Batch # E070813, Manufactured in 2008; and Batch # E0311002, Manufactured in 2011) [4]. None of which is the test lot used in its fed BE study 2011-2545. The reviewer examined the test formulation and found that both formulations **do not meet** the criteria for the *in vitro* option recommended in the draft guidance for Omega-3 Acid Esters Capsules. In addition, the firm stated:

"Please note that Par has manufactured an additional batch of the test formulation in 2013 (Batch # E041301) which contains the recommended labeled concentration for total omega-3-acid ethyl esters (i.e., (b) (4) %) and antioxidant, alpha-tocopherol (i.e., (b) (4) mg/g). Batch information and data will be submitted to the ANDA in the August time frame when stability data are available".

3. On November 1, 2013, the firm submitted additional formulation information of the newly manufactured batch as well as additional Quantitative Capsule Rupture Test (QCRT) data (DARRTS 11/01/2013 Quality/Response To Information Request; Bioequivalence/Response to Information Request). The firm's newly formulated product, lot No. 251302, meets the criteria for the *in vitro* option recommended in the draft guidance for Omega-3 Acid Esters Capsules. **The firm's formulation is adequate from the bioequivalence point of view**

[3] DARRTS. Search Terms: ANDA 091018 06/12/2013 COR-ANDADE-01(Bio Incomplete Deficiencies)
[4] DARRTS. Search Terms: ANDA 091018 06/25/2013 Bioequivalence/Response to Information Request

Quantitative capsule rupture test (QCRT):

4. The DBI previously reviewed the firm's QCRT and deemed the firm's test method and data acceptable[5]. The firm acknowledged the following FDA recommended method and specifications on August 26, 2010[6].

Medium	5% Triton X-100 in water with 1% pancreatin
Volume	900 mL
Temperature	37°C
USP Apparatus	II (paddles)
Rotational Speed	75 rpm
Specification	NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 60 minutes

5. In the November 1, 2013 submission, the firm submitted a different QCRT method for its newly reformulated test product; this method was not the previously reviewed and approved QCRT method. The firm developed its own method and conducted QCRT with the new method for the ***in vivo*** **study waiver request**:

Apparatus:	USP IV, Flow-through Cell
Flow:	2.0 mL/minute
Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specification	The firm did not propose specification.

In the same submission, the firm also conducted dissolution testing with a different method for **finished product release testing** and proposed specifications for the test drug product:

Medium	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket)
Rotational Speed	100 rpm
Specification	NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in (b)(4) minutes (b)(4)

[5] DARRTS. Search Terms ANDA 91018 08/11/2010 REV-BIOEQ-02(Dissolution Review)
[6] DARRTS. Search Terms ANDA 91018 08/26/2010 Bioequivalence/Response to Information Request

4 SUBMISSION SUMMARY

4.1 Drug Product Information[7]

Test Product	Omega-3-Acid Ethyl Esters Capsules, 1 gm
Reference Product	Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1 gm
RLD Manufacturer	Smithkline Beecham
NDA No.	021654
RLD Approval Date	10 November 2004
Indication[8]	LOVAZA is a combination of ethyl esters of omega 3 fatty acids, principally EPA and DHA, indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

4.2 PK/PD Information[8]

Bioavailability	Essential fatty acids (EFAs) are distributed widely and found stored within cells, primarily adipose tissue, throughout the body.
Food Effect	Serum concentrations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) appear to increase in relation to increased dietary consumption.
Tmax	Not provided.
Metabolism	The metabolic fate of fish oils after oral absorption includes formation into eicosanoids (prostaglandins, leukotrienes, lipoxins, etc.), esterification and hydrolysis from tissue glycerolipids, and elongation and desaturation to a variety of polyunsaturated fatty acids (PUFAs).
Excretion	Fatty acids are eliminated primarily by oxidative catabolism to carbon dioxide and water; small quantities are lost when skin and digestive cells are sloughed.
Half-life	Not provided.
Dosage and Administration	4 x 1 gram/day
Maximum Daily Dose	4 gram
Drug Specific Issues (if any)	N/A

[7] Electronic Orange Book, last accessed: 12/13/2013.
[8] http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=5ada82f0-a5fd-46c9-aecc-f106f614c9f0 (revised 09/2013)

4.3 OGD Recommendations for Drug Product

Number of studies recommended:	1 In Vitro Study or 2 In Vivo Studies

Option 1 In Vitro Testing Option (Provided that the test product exhibits pharmaceutical equivalence and similarity of inactive ingredients to the RLD product as specified in Appendices I and II of the Draft Guidance on Omega-3-Acid Ethyl Esters)

1.	**Type of study:**	Quantitative Capsule Rupture Test
	Design:	See Additional Comments
	Strength:	See Additional Comments
	Subjects:	N/A
	Additional Comments:	A quantitative capsule rupture test 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 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[9], USP Apparatus 4 (flow-through 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 drugs are cell) has been shown to be the most appropriate apparatus for drugs with poor solubility, compared with 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 Omega-3-Acid Ethyl Esters Capsule 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 (paddle) may be developed in conjunction with the method using USP Apparatus 4 for comparison, if desired. The data from USP Apparatus 4, and from USP Apparatus 2 (if conducted), should be submitted to the Division of Bioequivalence for evaluation and for determination of the most suitable method. The firm should provide all dissolution method development data showing that the dissolution method(s) studied have been systematically optimized for (but not limited to) the following parameters: 1. Dissolution 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))

[9] 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.*

		6. Flow rate (USP Apparatus 4 (flow-through cell) 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 5 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 6 dosage units for each determination. For final testing using the optimized method, 12 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[10] be used in the testing. For USP Apparatus 2, when used for this dosage form, the sampling probes should remain immersed in the dissolution 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.

Option 2 (In vivo option: Provided equivalence of API is established by meeting the qualitative and/or quantitative criteria specified in the Appendix I of the Draft Guidance on Omega-3-Acid Ethyl Esters)

1.	**Type of study:**	Fasting
	Design:	Single-dose, partial or fully replicated crossover *in-vivo*
	Strength:	1 gram contains at least 900 mg of the ethyl esters of Omega-3 fatty acids (Dose: 4×1 gram capsules)
	Subjects:	Healthy males and nonpregnant females, general population.
	Additional Comments	(1) In using the reference-scaled average bioequivalence approach for Omega-3-Acid Ethyl Esters capsules, please provide evidence 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, please refer to the draft Progesterone Oral Capsule Guidance at

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

		http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf. (2) We recommend that the applicant **control the subjects' diet from at least 48 hr prior to till at least 36 hr after drug administration. We recommend EPA and DHA limited meals throughout the diet control period**. (3) We recommend that baseline measures be calculated from an average of three or more (>3) samples collected between 24 and 0 hours (inclusive) prior to dosing.

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

Analytes to measure (in plasma/serum/blood):	(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 (9) EPA ethyl esters in plasma – Fed Study ONLY (10) DHA ethyl esters in plasma – Fed Study ONLY
Bioequivalence based on:	**<u>Fasting Study (90% CI)</u>** (1) Baseline-adjusted EPA total lipids (2) Baseline-adjusted DHA total lipids Please 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 **<u>Fed Study (90% CI)</u>** (1) EPA ethyl esters (2) DHA ethyl esters Please 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
Waiver request of in-vivo testing:	N/A

Source of most recent recommendations:	Draft Guidance on Omega-3-Acid Ethyl Esters Capsules (recommended Sep. 2012), available at the FDA website of BE Recommendations for Specific Products at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
Summary of OGD or DBE History:	**Controls:** There were several control documents for this drug product indicating a Open" or "Closed" status. Please see the following site for details: Internal Control Correspondence Database: http://cdsogd1/controls/DOCGRID.ASP Last accessed: 08/20/2013 **ANDAs** In addition to the current ANDA, the following ANDAs have been submitted for review:

ANDA #	Firm	Status
		(b) (4)
091028	Teva	Complete response
204940	Amneal	Pending
		(b) (4)
090973	Apotex	Pending

The following protocols[11] have been submitted for review:

Protocol #	Firm	Status
08-063		(b) (4)
11-039		
10-056		
10-059		

[11] DBE Protocol Database (b) (4) Last accessed 08/20/2013

4.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting and fed (pilot study)	Yes	01 each
Single-dose fed (pivotal)	Yes	2
Steady-state	No	--
In vitro dissolution	Yes	1
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	Yes	1
Amendments	Yes	5

4.5 Pre-Study Bioanalytical Method Validation

Fasting Pharmacokinetic Study (2008-1806)-Pilot Study

Table 1 Bioanalytical Method Validation ((b) (4))

Information Requested	Data
Bioanalytical method validation report location	Pages 1-113 and (b) (4) Amendment No. 3
Analyte	free eicosapentaenoic acid and free docosahexaenoic acid
Internal standard (IS)	(b) (4)
Method description	Protein precipitation; liquid chromatographic (LC) tandem mass spectrometric detection (MSMS) method
Limit of quantitation	10.0 ng/mL
Average recovery of Free EPA (%) QC A, QC B and QC C:	131.9 % to 140.0 %
Average recovery of Free EPA (%) QC E, QC F and QC G:	96.3 % to 107.4 %
Average recovery of Free DHA (%) QC A, QC B and QC C:	130.2 % to 135.8 %
Average recovery of Free DHA (%) QC E, QC F and QC G:	95.4 % to 103.3 %
Average recovery of IS (%)	124.1 %
Standard curve concentrations (units/mL)	10.00, 20.00, 50.00, 125.0, 350.0, 750.0, 1500, 3000 and 5000 ng/mL
QC concentrations (units/mL)	30.00 ng/mL (QC A), 400.0 ng/mL (QC B), 4000 ng/mL (QC C) for both EPA and DHA. 175 (QC E), 1952 ng/mL (QC F) and 3583 ng/mL (QC G) for EPA 669 (QC E), 1816 ng/mL (QC F) and 3668 ng/mL (QC G) for DHA
QC Intraday precision range (%)	2.5 to 8.1 % for EPA
QC Intraday accuracy range (%)	86.9 to 111.5 % for EPA
QC Intraday precision range (%)	2.5 to 8.7 % for DHA
QC Intraday accuracy range (%)	94.2 to 111.6 % for DHA
QC Interday precision range (%)	2.1 to 5.7 % for EPA
QC Interday accuracy range (%)	98.9 to 106.5 %. for EPA
QC Interday precision range (%)	2.4 to 6.0 % for DHA
QC Interday accuracy range (%)	100.3 to 106.5 % for DHA
Bench-top stability (hrs)	6.25 hours @ room temperature
Stock stability (days)	58 days @ -25°C ± 10°C
Processed stability (hrs)	56.50 hours @ approximately 5°C
Freeze-thaw stability (cycles)	6 cycles @ -70°C± 10°C
Long-term storage stability (days)	80 days @ -70°C ± 10°C
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	Selectivity was not established due to endogenous levels.

Fed Pharmacokinetic Study (2008-1807-Pilot Study)

Table 2 Bioanalytical Method Validation ((b) (4))

Information Requested	Data
Bioanalytical method validation report location	1-107 and (b) (4) Amendment No. 2
Analyte	Eicosapentaenoic acid and docosahexaenoic acid
Internal standard (IS)	(b) (4)
Method description	Protein precipitation; liquid chromatographic (LC) tandem mass spectrometric detection (MSMS) method
Limit of quantitation	1.00 µg/mL
Average recovery of EPA (%)	102.8 % to 116.1 %
Average recovery of DHA (%)	91.4 % to 111.0 %
Average recovery of IS (%)	92.5 %
Standard curve concentrations (units/mL)	1.00, 2.00, 5.00, 10.0, 25.0, 50.0, 100 and 150 µg/mL
QC concentrations (units/mL)	3.00 µg/mL (QC A), 20.0 µg/mL (QC B), 120 µg/mL (QC C) for both EPA and DHA. 6.12 µg/mL (QC E), 63.1 µg/mL (QC F) and 99.3 µg/mL (QCG) for EPA 25.8 µg/mL (QC E), 56.7 µg/mL (QC F) and 91.9 µg/mL (QCG) for DHA
QC Intraday precision range (%)	3.5 to 5.8 % for EPA
QC Intraday accuracy range (%)	90.6 to 107.5 % for EPA
QC Intraday precision range (%)	3.3 to 5.6 % for DHA
QC Intraday accuracy range (%)	90.1 to 107.5 % for DHA
QC Interday precision range (%)	2.7 to 4.2 % for EPA
QC Interday accuracy range (%)	96.5 to 104.2 %. for EPA
QC Interday precision range (%)	2.9 to 4.9 % for DHA
QC Interday accuracy range (%)	98.1 to 103.3 % for DHA
Bench-top stability (hrs)	5.00 hours @ room temperature
Stock stability (days)	41 days @ -25°C ± 10°C
Processed stability (hrs)	57.00 hours @ approximately 5°C
Freeze-thaw stability (cycles)	5 cycles @ -70°C± 10°C
Long-term storage stability (days)	63 days @ -70°C ± 10°C
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	Selectivity was not established due to endogenous levels.

Fed Bioequivalence Study (2008-1835)-Pivotal Study

Table 3 Bioanalytical Method Validation ((b) (4))

Information Requested	Data
Bioanalytical method validation report location	1-107
Analyte	Eicosapentaenoic acid and docosahexaenoic acid
Internal standard (IS)	(b) (4)
Method description	Protein precipitation; liquid chromatographic (LC) tandem mass spectrometric detection (MSMS) method
Limit of quantitation	1.00 µg/mL
Average recovery of EPA (%)	102.8 % to 116.1 %
Average recovery of DHA (%)	91.4 % to 111.0 %
Average recovery of IS (%)	92.5 %
Standard curve concentrations (units/mL)	1.00, 2.00, 5.00, 10.0, 25.0, 50.0, 100 and 150 µg/mL
QC concentrations (units/mL)	3.00 µg/mL (QC A), 20.0 µg/mL (QC B), 120 µg/mL (QC C) for both EPA and DHA. 6.12 µg/mL (QC E), 63.1 µg/mL (QC F) and 99.3 µg/mL (QC G) for EPA 25.8 µg/mL (QC E), 56.7 µg/mL (QC F) and 91.9 µg/mL (QC G) for DHA
QC Intraday precision range (%)	3.5 to 5.8 % for EPA
QC Intraday accuracy range (%)	90.6 to 107.5 % for EPA
QC Intraday precision range (%)	3.3 to 5.6 % for DHA
QC Intraday accuracy range (%)	90.1 to 107.5 % for DHA
QC Interday precision range (%)	2.7 to 4.2 % for EPA
QC Interday accuracy range (%)	96.5 to 104.2 %. for EPA
QC Interday precision range (%)	2.9 to 4.9 % for DHA
QC Interday accuracy range (%)	98.1 to 103.3 % for DHA
Bench-top stability (hrs)	5.00 hours @ room temperature
Stock stability (days)	In progress
Processed stability (hrs)	57.00 hours @ approximately 5°C
Freeze-thaw stability (cycles)	5 cycles @ -70°C± 10°C
Long-term storage stability (days)	In progress
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	Selectivity was not established due to endogenous levels.

Fed Bioequivalence Study (2011-2545)

Table 4 Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	16.5 Analytical Report, Pages 5315-5445
Analytes	Eicosapentaenoic Acid (EPA) Docosahexaenoic Acid (DHA)
Internal standard (IS)	(b) (4)
Method description	Hydrolysis followed by protein precipitation; liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method
Limit of quantitation	1.00 µg/mL for both EPA and DHA
Average recovery of drug (%)	91.1 % to 103.9 % for EPA 95.6 % to 104.2 % for DHA
Average recovery of IS (%)	99.2 %
Standard curve concentrations (units/mL)	1.00, 2.00, 5.00, 10.0, 25.0, 50.0, 100 and 150 µg/mL for both EPA and DHA
QC concentrations (units/mL)	QC A: 3.00 µg/mL, QC B: 60.0 µg/mL, QC C: 120 µg/mL QC E: 6.54 µg/mL, QC F: 56.5 µg/mL, QC G: 117 µg/mL for EPA QC A: 3.00 µg/mL, QC B: 60.0 µg/mL, QC C: 120 µg/mL QC E: 32.4 µg/mL, QC F: 62.0 µg/mL, QC G: 122 µg/mL for DHA
QC Intraday precision range (%)	0.7 % to 3.6 % for EPA 0.6 % to 3.6 % for DHA
QC Intraday accuracy range (%)	92.7 % to 108.1 % for EPA 92.6 % to 103.3 % for DHA
QC Interday precision range (%)	1.9 % to 5.5 % for EPA 1.8 % to 3.4 % for DHA
QC Interday accuracy range (%)	95.0 % to 103.3 % for EPA 95.1 % to 101.7 % for DHA
Bench-top stability (hrs)	19.50 hours @ room temperature
Stock stability (days)	In progress
Processed stability (hrs)	68.50 hours @ approximately 5°C
Freeze-thaw stability (cycles)	3 cycles -70 ± 10°C
Long-term storage stability (days)	In progress
Dilution integrity	Concentration diluted 5-fold and 2-fold
Selectivity	Not Applicable

Table 5 Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	16.5 Analytical Report, Pages 5446-5575
Analytes	Eicosapentaenoic Acid (EPA) Docosahexaenoic Acid (DHA)
Internal standard (IS)	(b) (4)
Method description	Protein precipitation; liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method
Limit of quantitation	10.0 ng/mL for EPA and DHA
Average recovery of drug (%)	113.6 % to 122.0 % for EPA 103.2 % to 106.7 % for DHA
Average recovery of IS (%)	114.6 %
Standard curve concentrations (units/mL)	10.0, 20.0, 50.0, 100, 200, 500, 1250 and 2500 ng/mL for EPA 10.0, 20.0, 50.0, 150, 400, 1000, 2500 and 5000 ng/mL for DHA
QC concentrations (units/mL)	QC A: 30.0, QC B: 1000, QC C: 2000, QC E: 139, QC F: 939, QC G: 1940 ng/mL for EPA QC A: 30.0, QC B: 2000, QC C: 4000, QC E: 382, QC F: 1980, QC G: 3880 ng/mL for DHA
QC Intraday precision range (%)	0.7 % to 10.9 % for EPA 0.8 % to 10.6 % for DHA
QC Intraday accuracy range (%)	97.1 % to 111.1 % for EPA 92.5 % to 108.3 % for DHA
QC Interday precision range (%)	2.3 % to 5.3 % for EPA 2.3 % to 4.6 % for DHA
QC Interday accuracy range (%)	99.8 % to 105.3 % for EPA 94.4 % to 105.3 % for DHA
Bench-top stability (hrs)	5.00 hours @ room temperature
Stock stability (days)	In Progress
Processed stability (hrs)	61.50 hours @ approximately 5°C
Freeze-thaw stability (cycles)	3 cycles @ -70 ± 10°C
Long-term storage stability (days)	In Progress
Dilution integrity	Concentration diluted 5-fold and 2-fold
Selectivity	Not Applicable

Table 6 Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	16.5 Analytical Report, Pages 5576-5685
Analytes	Eicosapentaenoic Acid (EPA) Docosahexaenoic Acid (DHA)
Internal standards (IS)	(b) (4)
Method description	Protein precipitation; liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method
Limit of quantitation	10.0 ng/mL for EPA and DHA
Average recovery of drug (%)	Not Applicable
Average recovery of IS (%)	Not Applicable
Standard curve concentrations (units/mL)	10.0, 20.0, 50.0, 100, 200, 500, 1250 and 2500 ng/mL for EPA 10.0, 20.0, 50.0, 150, 400, 1000, 2500 and 5000 ng/mL for DHA
QC concentrations (units/mL)	QC A: 30.0, QC B: 1000, QC C: 2000, QC E: 78.4, QC F: 878, QC G: 1880 ng/mL for EPA QC A: 30.0, QC B: 2000, QC C: 4000, QC E: 243, QC F: 1840, QC G: 3740 ng/mL for DHA
QC Intraday precision range (%)	0.4 % to 6.5 % for EPA 0.7 % to 6.4 % for DHA
QC Intraday accuracy range (%)	92.1 % to 107.7 % for EPA 91.5 % to 106.7 % for DHA
QC Interday precision range (%)	1.9 % to 4.7 % for EPA 2.1 % to 4.6 % for DHA
QC Interday accuracy range (%)	93.9 % to 105.0 % for EPA 93.7 % to 105.0 % for DHA
Bench-top stability (hrs)	18.75 hours on Ice
Stock stability (days)	In Progress
Processed stability (hrs)	95.50 hours @ approximately 5°C
Freeze-thaw stability (cycles)	5 cycles @ -70 ± 10°C
Long-term storage stability (days)	In Progress
Dilution integrity	Concentration diluted 5-fold and 2-fold
Selectivity	Not Applicable

Comments on the Pre-Study Method Validation:

The pre-study validation data are included in the review for information only and are not reviewed in detail at this time.

4.6 In Vivo Studies

Table 7. Summary of all in vivo Bioequivalence Studies

Fasting Pharmacokinetic Study (2008-1806)-Pilot Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (CV%)			Study Report Location
					Cmax (µg/mL)	Tmax (hr)	AUC0-t (µg*h/mL)	
Eicosapentaenoic acid (total lipids)								
2008-1806	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting Conditions	Pharmacokinetic single-dose study	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0031]	6 completing (1M/5F) Healthy subjects 34 (25-40)	3.19 (27) 3.23 (55)	12.00 (6.00-16.07) 9.50 (7.00-24.03) Median (Range)	47.36 (35) 49.09 (66)	2.0 Synopsis p. #3
Docosahexaenoic acid (total lipids)								
2008-1806	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting Conditions	Pharmacokinetic single-dose study	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0031]	6 completing (1M/5F) Healthy subjects 34 (25-40)	5.58 (39) 7.66 (37)	10.00 (3.05-12.00) 7.50 (2.00-24.03) Median (Range)	50.48 (99) 78.92 (50)	2.0 Synopsis p. #3
Eicosapentaenoic acid (free fatty acids)								
2008-1806	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting Conditions	Pharmacokinetic single-dose study	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0031]	6 completing (1M/5F) Healthy subjects 34 (25-40)	0.081 (45) 0.070 (50)	4.00 (3.00-4.00) 4.00 (2.00-24.03) Median (Range)	0.349 (37) 0.447 (50)	2.0 Synopsis p. #4
Docosahexaenoic acid (free fatty acids)								
2008-1806	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting Conditions	Pharmacokinetic single-dose study	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0031]	6 completing (1M/5F) Healthy subjects 34 (25-40)	0.581 (58) 0.498 (43)	4.00 (3.00-4.00) 4.00 (3.00-24.03) Median (Range)	2.387 (57) 3.128 (52)	2.0 Synopsis p. #4

Fed Pharmacokinetic Study (2008-1807-Pilot Study)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (CV%)			Study Report Location
					Cmax (µg/mL)	Tmax (hr)	AUC0-t (µg*h/mL)	
Eicosapentaenoic acid (total lipids)								
2008-1807	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fed Conditions	Pharmacokinetic single-dose study	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0031]	6 completing (1M/5F) Healthy subjects 33 (20-45)	51.89 (29) 58.98 (34)	11.00 (5.00-16.00) 8.00 (7.00-10.00) Median (Range)	820.75 (25) 775.36 (32)	2.0 Synopsis p. #3
Docosahexaenoic acid (total lipids)								
2008-1807	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fed Conditions	Pharmacokinetic single-dose study	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0031]	6 completing (1M/5F) Healthy subjects 33 (20-45)	29.12 (40) 34.74 (55)	8.50 (3.00-10.00) 7.00 (5.00-10.00) Median (Range)	277.28 (42) 219.70 (52)	2.0 Synopsis p. #3
Eicosapentaenoic acid (free fatty acids)								
2008-1807	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fed Conditions	Pharmacokinetic single-dose study	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0031]	6 completing (1M/5F) Healthy subjects 33 (20-45)	0.516 (33) 0.682 (21)	8.00 (3.00-10.00) 8.00 (7.00-9.00) Median (Range)	3.778 (30) 4.083 (13)	2.0 Synopsis p. #4
Docosahexaenoic acid (free fatty acids)								
2008-1807	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fed Conditions	Pharmacokinetic single-dose study	Lovaza™, 1000 mg, Capsules p.o. [Lot # 7HH0031]	6 completing (1M/5F) Healthy subjects 33 (20-45)	1.424 (37) 1.849 (23)	8.50 (3.00-10.00) 7.50 (7.00-9.00) Median (Range)	8.213 (35) 8.773 (20)	2.0 Synopsis p. #4

Fed Bioequivalence Study (2008-1835)-Pivotal Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (CV%)			Study Report Location
					Cmax (µg/mL)	Tmax (hr)	AUC0-t (µg*h/mL)	
Eicosapentaenoic acid (total lipids)								
2008-1835	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters 1000 mg Capsules under Fed Conditions	Randomized single-dose crossover	Omega-3-Acid Ethyl Esters, 1000 mg Capsules, p.o. [Lot # 21680902] Lovaza™, 1000 mg, Capsules p.o. [Lot # 803040W]	70 completing (43M/27F) Healthy subjects 35 (21-53)	79.48 (43) 69.40 (40)	6.02 (4.00-72.00) 6.00 (4.00-20.00) Median (Range)	1720.51 (31) 1575.52 (30)	2.0 Synopsis p. #4
Docosahexaenoic acid (total lipids)								
2008-1835	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters 1000 mg Capsules under Fed Conditions	Randomized single-dose crossover	Omega-3-Acid Ethyl Esters, 1000 mg Capsules, p.o. [Lot # 21680902] Lovaza™, 1000 mg, Capsules p.o. [Lot # 803040W]	70 completing (43M/27F) Healthy subjects 35 (21-53)	51.43 (55) 46.66 (49)	6.00 (3.00-72.00) 6.00 (3.00-48.00) Median (Range)	822.68 (43) 761.88 (46)	2.0 Synopsis p. #4

Fed Bioequivalence Study (2011-2545)-Pivotal Study

Eicosapentaenoic Acid from Total Lipids											
					Mean Parameters (CV%)						
Study Ref. No.	*Study Objective*	*Study Design*	*Treatments (Dose, Product ID, Dosage Form, Route)*	*Subjects (No. M/F) Age:mean(range)*	*Cmax (µg/mL)*	*Tmax (hr)*	*AUC0-72 (h.µg/mL)*	*AUCo-∞ (h.µg/mL)*	*T½ (h)*	*Kel (1/h)*	*Study Report Location*
2011-2545	A Single-Dose, Replicate, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters 1000 mg Capsules under Fed Conditions	Randomized, single-dose, crossover	Dose: 4 x 1000 mg A: Omega-3 acid ethyl esters 1000 mg capsules, Lot No.: E03110201 (Par Pharmaceutical, Inc., USA)) p.o.	45 healthy subjects (30 M/15 F) 36 years (20- 55)	52.26 (44)	Median 6.00 (3.00- 48.00)	1322.55 (39)	N/A	N/A	N/A	Sections 2.0 and 16.2.6
			Dose: 4 x 1000 mg B: Lovaza® 1000 mg capsules, Lot No.: 1ZP6604 (GlaxoSmithKline, RTP, USA) p.o.		51.98 (40)	Median 6.00 (3.00- 72.00)	1334.77 (36)	N/A	N/A	N/A	Sections 2.0 and 16.2.6

Docosahexaenoic Acid from Total Lipids											
					Mean Parameters (CV%)						
Study Ref. No.	*Study Objective*	*Study Design*	*Treatments (Dose, Product ID, Dosage Form, Route)*	*Subjects (No. M/F) Age:mean(range)*	*Cmax (µg/mL)*	*Tmax (hr)*	*AUC0-72 (h.µg/mL)*	*AUCo-∞ (h.µg/mL)*	*T½ (h)*	*Kel (1/h)*	*Study Report Location*
2011-2545	A Single-Dose, Replicate, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters 1000 mg Capsules under Fed Conditions	Randomized, single-dose, crossover	Dose: 4 x 1000 mg A: Omega-3 acid ethyl esters 1000 mg capsules, Lot No.: E03110201 (Par Pharmaceutical, Inc., USA)) p.o.	45 healthy subjects (30 M/15 F) 36 years (20- 55)	33.17 (48)	Median 6.00 (2.00- 72.20)	643.40 (50)	N/A	N/A	N/A	Sections 2.0 and 16.2.6
			Dose: 4 x 1000 mg B: Lovaza® 1000 mg capsules, Lot No.: 1ZP6604 (GlaxoSmithKline, RTP, USA) p.o.		32.21 (46)	Median 6.00 (2.00- 72.03)	608.15 (40)	N/A	N/A	N/A	Sections 2.0 and 16.2.6

Eicosapentaenoic Acid from Free Fatty Acids											
					Mean Parameters (CV%)						
Study Ref. No.	***Study Objective***	***Study Design***	***Treatments (Dose, Product ID, Dosage Form, Route)***	***Subjects (No. M/F) Age:mean(range)***	***Cmax (ng/mL)***	***Tmax (hr)***	***AUC0-72 (h.ng/mL)***	***AUCo-∞ (h.ng/mL)***	***T½ (h)***	***Kel (1/h)***	***Study Report Location***
2011-2545	A Single-Dose, Replicate, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters 1000 mg Capsules under Fed Conditions	Randomized, single-dose, crossover	Dose: 4 x 1000 mg A: Omega-3 acid ethyl esters 1000 mg capsules, Lot No.: E03110201 (Par Pharmaceutical, Inc., USA)) p.o.	45 healthy subjects (30 M/15 F) 36 years (20- 55)	633.5 (44)	Median 5.00 (4.00- 20.00)	5741.2 (40)	N/A	N/A	N/A	Sections 2.0 and 16.2.6
			Dose: 4 x 1000 mg B: Lovaza® 1000 mg capsules, Lot No.: 1ZP6604 (GlaxoSmithKline, RTP, USA) p.o.		645.6 (44)	Median 6.00 (3.00- 72.03)	5622.6 (40)	N/A	N/A	N/A	Sections 2.0 and 16.2.6
Docosahexaenoic Acid from Free Fatty Acids											
					Mean Parameters (CV%)						
Study Ref. No.	***Study Objective***	***Study Design***	***Treatments (Dose, Product ID, Dosage Form, Route)***	***Subjects (No. M/F) Age:mean(range)***	***Cmax (ng/mL)***	***Tmax (hr)***	***AUC0-72 (h.ng/mL)***	***AUCo-∞ (h.ng/mL)***	***T½ (h)***	***Kel (1/h)***	***Study Report Location***
2011-2545	A Single-Dose, Replicate, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters 1000 mg Capsules under Fed Conditions	Randomized, single-dose, crossover	Dose: 4 x 1000 mg A: Omega-3 acid ethyl esters 1000 mg capsules, Lot No.: E03110201 (Par Pharmaceutical, Inc., USA)) p.o.	45 healthy subjects (30 M/15 F) 36 years (20- 55)	1951.7 (47)	Median 5.00 (3.00- 72.00)	17645.1 (58)	N/A	N/A	N/A	Sections 2.0 and 16.2.6
			Dose: 4 x 1000 mg B: Lovaza® 1000 mg capsules, Lot No.: 1ZP6604 (GlaxoSmithKline, RTP, USA) p.o.		1953.5 (46)	Median 6.00 (3.00- 72.03)	16497.9 (60)	N/A	N/A	N/A	Sections 2.0 and 16.2.6

Table 8. Statistical Summary of the Comparative Bioavailability Data Calculated by the Firm

Fed Bioequivalence Study (2011-2545)

Eicosapentaenoic Acid from Total Lipids						
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (2011-2545)						
Parameter	*Test*	*Ref*	*Ratio (%)*	*90% C.I.*	*Intra-Sub Within Ref SD (s_{WR})*	*95% Upper Bound for RSABE Criterion*
Cmax	47.61	48.04	99.09	93.45-105.08	0.197	N/A
AUC0-72	N/A	N/A	98.37	N/A	0.378	-0.081717
Docosahexaenoic Acid from Total Lipids						
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (2011-2545)						
Parameter	*Test*	*Ref*	*Ratio (%)*	*90% C.I.*	*Intra-Sub Within Ref SD (s_{WR})*	*95% Upper Bound for RSABE Criterion*
Cmax	29.54	29.14	101.37	93.99-109.33	0.231	N/A
AUC0-72	N/A	N/A	103.08	N/A	0.339	-0.060883

Eicosapentaenoic Acid from Free Fatty Acids				
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (2011-2545)				
Parameter	*Test*	*Ref*	*Ratio (%)*	*90% C.I.*
Cmax	568.1	585.0	97.12	90.70-103.99
AUC0-72	5320.1	5227.7	101.77	95.93-107.96
Docosahexaenoic Acid from Free Fatty Acids				
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (2011-2545)				

Parameter	*Test*	*Ref*	*Ratio (%)*	*90% C.I.*	*Intra-Sub Within Ref SD (s_{WR})*	*95% Upper Bound for RSABE Criterion*
Cmax	N/A	N/A	95.79	N/A	0.313	-0.051539
AUC0-72	N/A	N/A	101.71	N/A	0.298	-0.048937

Reviewer's Comments:

The study results calculated by the firm meet the acceptable BE limit for the EPA and DHA from total lipids and EPA and DHA from free fatty acids. However, the firm did not measure the analytes recommended in the current draft guidance for Omega-3-Acid Ethyl Esters Capsules. In addition, the firm did not provide data on a fasting BE study

(per the Guidance, a fasting BE study is recommended). The "*In Vivo* Studies" of the application is **inadequate.**

Table 9. Reanalysis of Study Samples

Fasting Pharmacokinetic Study (2008-1806)-Pilot Study

Study No. 2008-1806 Additional information, 16.5 Analytical Report Pages 25-34								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Eicosapentaenoic Acid (Total Lipids)								
Pharmacokinetic[1]	NA	4	NA	1.75	NA	0	NA	0
Total	**NA**	**4**	**NA**	**1.75**	**NA**	**0**	**NA**	**0**
Docosahexaenoic Acid (Total Lipids)								
Pharmacokinetic[1]	NA	4	NA	1.75	NA	0	NA	0
Total	**NA**	**4**	**NA**	**1.75**	**NA**	**0**	**NA**	**0**

Fed Pharmacokinetic Study (2008-1807-Pilot Study)

Study No. 2008-1807 Additional information, 16.5 Analytical Report Pages 24-34								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Eicosapentaenoic Acid (Free Fatty Acids)								
UISR	NA	4	NA	1.75	NA	0	NA	0
Total	NA	4	NA	1.75	NA	0	NA	0
Docosahexaenoic Acid (Free Fatty Acids)								
UISR	NA	4	NA	1.75	NA	0	NA	0
Total	**NA**	**4**	**NA**	**1.75**	**NA**	**0**	**NA**	**0**

Fed Bioequivalence Study (2008-1835)-Pivotal Study

Study No. 2008-1835 Additional information, 16.5 Analytical Report Pages 69-126								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Eicosapentaenoic Acid (Total Lipids)								
Pharmacokinetic[1]	6	4	0.41	0.27	1	0	0.07	0
AULOQ	6	9	0.41	0.61	6	9	0.41	0.61
IE	1	0	0.07	0	1	0	0.07	0
UISR	2	4	0.14	0.27	2	4	0.14	0.27
Total	**15**	**17**	**1.02**	**1.16**	**10**	**13**	**0.68**	**0.88**
Docosahexaenoic Acid (Total Lipids)								
Pharmacokinetic[1]	0	0	0	0	0	0	0	0

AULOQ	11	19	0.75	1.29	11	19	0.75	1.29
IE	1	0	0.07	0	1	0	0.07	0
UISR	2	4	0.14	0.27	2	4	0.14	0.27
Total	**14**	**23**	**0.95**	**1.56**	**14**	**23**	**0.95**	**1.56**
Eicosapentaenoic Acid (Free Fatty Acids)								
Pharmacokinetic[1]	1	0	0.07	0	1	0	0.07	0
EE	1	1	0.07	0.07	1	1	0.07	0.07
INE	7	0	0.48	0	7	0	0.48	0
UISR	48	35	3.27	2.38	48	35	3.27	2.38
Total	**57**	**36**	**3.88**	**2.45**	**57**	**36**	**3.88**	**2.45**
Docosahexaenoic Acid (Free Fatty Acids)								
Pharmacokinetic[1]	0	0	0	0	0	0	0	0
AULOQ	2	2	0.14	0.14	2	2	0.14	0.14
EE	1	1	0.07	0.07	1	1	0.07	0.07
INE	7	0	0.48	0	7	0	0.48	0
UISR	48	35	3.27	2.38	48	35	3.27	2.38
Total	**58**	**38**	**3.95**	**2.59**	**58**	**38**	**3.95**	**2.59**

Fed Bioequivalence Study (2011-2545)-Pivotal Study

Study No.: 2011-2545 *Additional information, 16.5 Analytical Report, Page(s): 49-51* *Analyte: Eicosapentaenoic Acid from Total Lipids*								
	Nr. of samples reanalyzed				*Nr. of recalculated values used after reanalysis*			
	Actual Nr.		*% of assays*		*Actual Nr.*		*% of assays*	
Reason why assay was repeated	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Pharmacokinetic	0	0	0	0	0	0	0	0
AULOQ	1	0	0.05	0	1	0	0.05	0
EE	4	1	0.22	0.06	4	1	0.22	0.06
Extreme IS	5	5	0.27	0.28	5	5	0.27	0.28
SNE	1	0	0.05	0	1	0	0.05	0
UISR	26	21	1.42	1.16	26	21	1.42	1.16
Total	**37**	**27**	**2.03**	**1.50**	**37**	**27**	**2.03**	**1.50**

Code	*Definition*
AULOQ	*Above the Upper Limit of Quantitation.*
EE	*Extraction Error*
Extreme IS	*Extreme Internal Standard Response*
SNE	*Sample Not Extracted*
UISR	*Unacceptable Internal Standard Response.*

Study No.: 2011-2545 Additional information, 16.5 Analytical Report, Page(s): 52-54 Analyte: Docosahexaenoic Acid from Total Lipids								
	Nr. of samples reanalyzed				Nr. of recalculated values used after reanalysis			
	Actual Nr.		% of assays		Actual Nr.		% of assays	
Reason why assay was repeated	A	B	A	B	A	B	A	B
Pharmacokinetic	0	0	0	0	0	0	0	0
EE	4	1	0.22	0.06	4	1	0.22	0.06
Extreme IS	5	5	0.27	0.28	5	5	0.27	0.28
SNE	1	0	0.05	0	1	0	0.05	0
UISR	26	21	1.42	1.16	26	21	1.42	1.16
Total	36	27	1.97	1.50	36	27	1.97	1.50

Code	Definition
EE	Extraction Error
Extreme IS	Extreme Internal Standard Response
SNE	Sample Not Extracted
UISR	Unacceptable Internal Standard Response.

Study No.: 2011-2545 Additional information, 16.5 Analytical Report, Page(s): 121-122 Analyte: Eicosapentaenoic Acid from Free Fatty Acids								
	Nr. of samples reanalyzed				Nr. of recalculated values used after reanalysis			
	Actual Nr.		% of assays		Actual Nr.		% of assays	
Reason why assay was repeated	A	B	A	B	A	B	A	B
Pharmacokinetic	0	0	0	0	0	0	0	0
EE	2	0	0.11	0	2	0	0.11	0
Extreme IS	4	2	0.22	0.11	4	2	0.22	0.11
UISR	8	3	0.44	0.17	8	3	0.44	0.17
Total	14	5	0.77	0.28	14	5	0.77	0.28

Code	Definition
EE	Extraction Error
Extreme IS	Extreme Internal Standard Response
UISR	Unacceptable Internal Standard Response.

Study No.: 2011-2545 *Additional information, 16.5 Analytical Report, Page(s): 123-124* *Analyte: Docosahexaenoic Acid from Free Fatty Acids*								
	Nr. of samples reanalyzed				*Nr. of recalculated values used after reanalysis*			
	Actual Nr.		*% of assays*		*Actual Nr.*		*% of assays*	
Reason why assay was repeated	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Pharmacokinetic	0	0	0	0	0	0	0	0
AULOQ	1	1	0.05	0.06	1	1	0.05	0.06
EE	2	0	0.11	0	2	0	0.11	0
Extreme IS	5	2	0.27	0.11	5	2	0.27	0.11
UISR	6	3	0.33	0.17	6	3	0.33	0.17
Total	**14**	**6**	**0.77**	**0.33**	**14**	**6**	**0.77**	**0.33**

Code	*Definition*
AULOQ	*Above the Upper Limit of Quantitation.*
EE	*Extraction Error*
Extreme IS	*Extreme Internal Standard Response*
UISR	*Unacceptable Internal Standard Response.*

Comments from the Reviewer:

The reanalysis data are for information only and not reviewed in detail at this time.

4.7 Formulation

Location in appendix	Section 5.2 Formulation Data
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**Yes**
If not acceptable, why?	N/A

4.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS, ANDA 091018: REV-BIOEQ-02(Dissolution Review), dated 05/04/2009, 02/04/2010, 08/11/2010 and 03/06/2014
Source of Method (USP, FDA or Firm)	Firm
Medium	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120k/L)
Volume (mL)	900 mL
USP Apparatus type	I (basket, 40 mesh)
Rotation (rpm)	100 rpm
DBE-recommended specifications	NLT (b)(4)% (Q) of each EPA and DHA is dissolved in 300 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	**Yes**
If not then why?	

Reviewer's Comment:

1. The DBI previously reviewed the firm's QCRT and deemed the firm's test method and data acceptable[12]. The firm acknowledged the following FDA recommended method and specifications on August 26, 2010[13].

Medium	5% Triton X-100 in water with 1% pancreatin
Volume	900 mL
Temperature	37°C
USP Apparatus	II (paddles)
Rotational Speed	75 rpm
Specification	NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 60 minutes

2. In the November 1, 2013 submission, the firm submitted a different QCRT method for its newly reformulated test product; this method was not the previously reviewed

[12] DARRTS. Search Terms ANDA 91018 08/11/2010 REV-BIOEQ-02(Dissolution Review)
[13] DARRTS. Search Terms ANDA 91018 08/26/2010 Bioequivalence/Response to Information Request

and approved QCRT method. The firm developed its own method and conducted QCRT with the new method for the ***in vivo*** **study waiver request**:

Apparatus:	USP IV, Flow-through Cell
Flow:	2.0 mL/minute
Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specification	The firm did not propose specification.

In the same submission, the firm also conducted dissolution testing with a different method for **finished product release testing** and proposed specifications for the test drug product:

Medium	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket)
Rotational Speed	100 rpm
Specification	NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in (b)(4) minutes (b)(4)

By comparing the drug release data using flow-through cell and basket in the amendment of 11/01/2013, as well as the data using paddle in the previous amendment, it is found that the methods with flow-through cell and basket, respectively, appear to be more discriminating than the paddle method. The drug release data and variability with flow-through cell and basket are comparable for both EPAee and DHAee. Considering the greater complexity of conducting QCRT using the flow-through cell apparatus, DBI accepts the firm's proposed basket method as the regulatory method for release and stability testing of the test product and recommended specifications of "NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)". (DARRTS, ANDA 091018: REV-BIOEQ-02(Dissolution Review) dated 03/06/2014)

4.9 Waiver Request(s)

Strengths for which waivers are requested	1 gram
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	No
Waivers granted?	**WAIVER GRANTED**
If not then why?	N/A

4.10 Deficiency Comments Related to the firm's Option of *in vitro* Studies

N/A

4.11 Recommendations

1. The *in vitro* QCRT conducted by Par Pharmaceuticals, Inc. on it's Omega-3 Acid Ethyl Esters Capsules, 1 g (batch # E041301), comparing with Smithkline Beecham's Lovaza® (Omega-3-Acid Ethyl Esters) Capsules, 1 g, (batch #1ZP0924) is acceptable.

2. The *in vivo* study waiver request for the test product, Omega-3 Acid Ethyl Esters Capsules, 1 g, is granted.

4.12 Comments for Other OGD Disciplines

None

5 APPENDIX

5.1 Individual Study Reviews

5.1.1 Single-dose Fasting Pharmacokinetic Study (2008-1806)—Pilot Study

5.1.1.1 Study Design

Table 10 Study Information

Study Number	2008-1806
Study Title	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting Conditions
Clinical Site (Name, Address, Phone #)	Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6 Phone: (416) 759-4111
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP (C)
Dosing Dates	August 07, 2008 and August 14, 2008
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	August 19, 2008 to October 17, 2008 (Free Eicosapentaenoic acid and Free Docosahexaenoic acid)
	August 19, 2008 to October 06, 2008 (Eicosapentaenoic acid and Docosahexaenoic acid)
Analytical Director	(b) (6) M.Sc.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Seventy-one (71) days (August 06, 2008 - October 16, 2008) (Free Eicosapentaenoic acid and Free Docosahexaenoic acid) Sixty-one (61) days (August 06, 2008 - October 06, 2008) (Eicosapentaenoic acid and Docosahexaenoic acid)

Table 11. Product information

Product	**Drug**
Treatment ID	N/A
Product Name	Lovaza™ 1000 mg Capsules
Manufacturer	Catalent Pharma Solutions, USA
Batch/Lot No.	Lot No.: 7HH0031
Manufacture Date	N/A
Expiration Date	NOV 2010
Strength	1000 mg
Dosage Form	Capsules
Bio-batch Size	N/A
Production Batch Size	N/A
Potency	N/A
Content Uniformity (min, max, mean)	N/A
Dose Administered	4 x 1000 mg
Route of Administration	Oral

Table 12. Study Design, Single-Dose Fasting PK Study-Pilot Study

Number of Subjects	Dosed, completed and analyzed: 06
No. of Sequences	1
No. of Periods	2
No. of Treatments	1
No. of Groups	1
Washout Period	7 days; Study drugs were administered on August 07, 2008 and on August 14, 2008, for Period 1 and Period 2, respectively.
Randomization Scheme	N/A; all 06 subjects received the same RLD product
Blood Sampling Times	Six pre-dose levels (of EPA and DHA) were measured over a 24-hour interval. All other blood samples were collected prior to drug administration and at -24 (x2), -21, -18, -15, -12, -1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, and 24 hours following drug administration in pre-chilled, labeled 10 mL blood collection tubes containing K2EDTA as the anticoagulant.
Blood Volume Collected/Sample	In each period, 20 blood samples from 19 time points were obtained from an arm vein of each subject by direct venipuncture or from an indwelling cannula. Approximately 425 mL of blood was collected from each subject over the course of the study, including the samples collected for screening and post-study tests
Blood Sample Processing/Storage	Blood samples were centrifuged at 3500 rpm for 8 minutes at approximately 4ºC, within 20 minutes of collection. After being centrifuged, at least 3 mL of the plasma was transferred into 3 labeled polypropylene tubes (3 x at least 1 mL). These tubes were flash frozen as soon as possible after separation. The time at which samples were placed into the solution for flash freezing was recorded. The plasma samples were flash frozen within 20 minutes from the time of sample collection. All samples were stored at -70ºC ± 10ºC or colder pending shipment. The stored samples were then transferred to the analytical facility.
IRB Approval	July 17, 2008
Informed Consent	May 29, 2008
Length of Fasting	4 x 1000 mg capsules administered after an overnight fast of at least 10 hours totaling 400 mg. Standardized EPA and DHA limited, xanthine-free meals with caffeine-free beverages were provided at least 4 hours after drug administration in each period.
Length of Confinement	Subjects were confined to the PMRI clinical facility from at least 34 hours prior to each drug administration until 24 hours post-dose.
Safety Monitoring	Vital signs were not measured throughout the study. Post-clinical laboratory tests for hematology, serum chemistry, and urinalysis and a post-study physical examination (including vital signs measurements), were performed.

Comments on Study Design:

The study design is acceptable.

5.1.1.2 Clinical Results

Table 13. Demographics Profile of Subjects Completing the Fasting PK Study-Pilot Study

Study No: 2008-1806		
		Treatment Groups
		N = 6
Age (years)	**Mean ± SD** **Range**	34 ± 6 25 - 40
Age Group	**< 18** **18 - 40** **41 - 64** **65 - 75** **> 75**	0 (0.0%) 6 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
Sex	**Male** **Female**	1 (16.7%) 5 (83.3%)
Race	**Asian** **Black** **Caucasian** **Hispanic/Latino** **Other**	2 (33.3%) 1 (16.7%) 3 (50.0%) 0 (0.0%) 0 (0.0%)
BMI	**Mean ± SD** **Range**	25.4 ± 3.7 21.2 - 30.0
Other Factors		N/A

Table 14. Dropout Information, Fasting PK Study-Pilot Study

No subjects withdrew or were dismissed from study 2008-1806.

Table 15. Study Adverse Events, Fasting PK Study-Pilot Study

There were no adverse events reported for study 2008-1806.

Table 16. Protocol Deviations, Fasting PK Study-Pilot Study

There were no protocol deviations in study 2008-1806. There were some blood sampling time deviations reported in the Section 16.2.2 Protocol Deviation Report, however, all deviations occurred less than 5% of the nominal time points, and thus considered to be insignificant. The firm used actual sampling times for its PK calculation and the reviewer used nominal times for its PK calculation.

5.1.1.3 Bioanalytical Results

Table 17. Assay Validation – Within the Fasting PK Study-Pilot Study

Bioequivalence Study No. 2008-1806 Free Eicosapentaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	2.3	3.8	1.2	0.6	2.8	0.4	0.5	0.5	0.3
Inter day Accuracy (%Actual)	100.0	101.5	96.2	98.4	100.3	102.5	100.3	103.0	97.8
Linearity	0.9995-0.9996								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1806 Free Eicosapentaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	400	4000	182	2240	4360
Inter day Precision (%CV)	4.1	2.8	3.0	3.3	1.6	3.6
Inter day Accuracy (%Actual)	100.0	102.3	101.4	88.5	90.9	93.2

Bioequivalence Study No. 2008-1806 Free Docosahexaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	5.3	10.2	0.7	1.7	3.2	3.8	2.8	0.2	1.7
Inter day Accuracy (%Actual)	98.3	104.0	97.8	101.6	100.3	98.3	99.3	101.2	100.0
Linearity	0.9983-0.9997								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1806 Free Docosahexaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	400	4000	707	2070	4190
Inter day Precision (%CV)	12.0	5.9	3.1	3.6	2.0	3.7
Inter day Accuracy (%Actual)	98.3	99.5	102.4	88.1	91.6	96.6

Bioequivalence Study No. 2008-1806 Eicosapentaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	3.2	3.0	1.9	1.0	1.6	0.4	0.8	0.4
Inter day Accuracy (%Actual)	99.7	95.0	102.6	104.0	97.2	104.6	95.9	101.3
Linearity	0.9994 -0.9995							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1806 Eicosapentaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (µg/mL)	3.00	20.0	120	6.12	63.1	99.3
Inter day Precision (%CV)	3.7	2.4	2.1	3.1	2.9	3.2
Inter day Accuracy (%Actual)	99.7	98.5	103.3	104.6	100.2	102.7

Bioequivalence Study No. 2008-1806 Docosahexaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	0.4	1.6	0.8	1.5	1.7	0.7	1.0	0.4
Inter day Accuracy (%Actual)	97.2	96.5	102.2	105.0	97.6	104.2	95.4	102.0
Linearity	0.9993-0.9996							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1806 Docosahexaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (µg/mL)	3.00	20.0	120	25.8	56.7	91.9
Inter day Precision (%CV)	2.4	2.4	1.3	1.2	2.4	2.5
Inter day Accuracy (%Actual)	99.3	98.5	103.3	102.3	102.1	105.2

Comments on Study Assay Validation:

The study validation data of the calibrators and quality control samples were not evaluated; the above information is provided for information purposes only.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially; EPA and DHA FFA: 4-6 EPA and DHA total lipids: 1-3

Comments on Chromatograms:

Chromatograms found on page 80 of 991 in the Fasting Analytical Report, Protocol No.: 2008-1806 Version: 1, A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fasting Conditions.

Table 18. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	Repeat Sample Analysis Procedure and Acceptance Criteria

Summary/Conclusions, Study Assays:

The PK study was not evaluated; this information is provided for information purposes only.

5.1.1.4 Pharmacokinetic Results

Table 19. Arithmetic Mean Pharmacokinetic Parameters

Not applicable. The reviewer did not review and reanalyze the BE study data.

Table 20. Geometric Means and 90% Confidence Intervals - Firm Calculated

Lovaza Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Pharmacokinetic Study (Study No. 2008-1806)				
Eicosapentaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	45.03	29.97	150.27	48.32 - 467.28
Cmax	3.10	2.69	115.13	66.08 - 200.60
Docosahexaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	38.06	68.05	55.94	29.82 - 104.93
Cmax	5.30	7.22	73.48	57.97 - 93.14
Eicosapentaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	0.327	0.393	83.17	59.05 - 117.16
Cmax	0.074	0.063	116.35	90.24 – 150.02
Docosahexaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	2.045	2.786	73.41	53.60 - 100.54
Cmax	0.500	0.455	109.95	84.04 - 143.85

Comments on Pharmacokinetic and Statistical Analysis:

Not applicable. The reviewer did not review and reanalyze the BE study data for verification.

Summary and Conclusions, Single-Dose Fasting PK Study-Pilot Study:

1. The firm included 6 subjects using the RLD product under fasting conditions for the final calculations of AUCt and Cmax of plasma free EPA and DHA fatty acids, and total EPA and DHA lipids, after baseline level adjustments.

2. The current application has not been fully evaluated due to the inadequacy of the information and data provided, therefore, the reviewer did not conduct statistical analyses for the pilot BE study under fasting conditions (with the RLD product).

5.1.2 Single-dose Fed Pharmacokinetic Study (2008-1807)-Pilot Study

5.1.2.1 Study Design

Table 21. Study Information

Study Number	2008-1807
Study Title	A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fed Conditions
Clinical Site (Name, Address, Phone #)	Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6 Phone: (416) 759-4111
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP (C)
Dosing Dates	August 07, 2008 and August 14, 2008
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	August 18, 2008 to October 20, 2008 (Free Eicosapentaenoic acid and Free Docosahexaenoic acid)
	August 18, 2008 to September 30, 2008 (Eicosapentaenoic acid and Docosahexaenoic acid)
Analytical Director	(b) (6) M.Sc.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Seventy-five (75) days (August 06, 2008 - October 20, 2008) (Free Eicosapentaenoic acid and Free Docosahexaenoic acid) Fifty-five (55) days (August 06, 2008 - September 30, 2008) (Eicosapentaenoic acid and Docosahexaenoic acid)

Table 22. Product Information

Product	Drug
Treatment ID	N/A
Product Name	Lovaza™ 1000 mg Capsules
Manufacturer	Catalent Pharma Solutions, USA
Batch/Lot No.	Lot No.: 7HH0031
Manufacture Date	N/A
Expiration Date	NOV 2010
Strength	1000 mg
Dosage Form	Capsules
Bio-batch Size	N/A
Production Batch Size	N/A
Potency	N/A
Content Uniformity (min, max, mean)	N/A
Dose Administered	4 x 1000 mg
Route of Administration	Oral

Table 23. Study Design, Single-Dose Fed PK Study-Pilot Study

No. of Subjects	Dosed, completed and analyzed: 06
No. of Sequences	1
No. of Periods	2
No. of Treatments	1
No. of Groups	1
Washout Period	7 days; Study drugs were administered on August 07, 2008 and on August 14, 2008, for Period 1 and Period 2, respectively.
Randomization Scheme	N/A; all 06 subjects received the same RLD product
Blood Sampling Times	Six pre-dose levels (of EPA and DHA) were measured over a 24-hour interval. All other blood samples were collected prior to drug administration and at -24 (x2), -21, -18, -15, -12, -1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, and 24 hours following drug administration in pre-chilled, labeled 10 mL blood collection tubes containing K2EDTA as the anticoagulant.
Blood Volume Collected/Sample	In each period, 20 blood samples from 19 time points were obtained from an arm vein of each subject by direct venipuncture or from an indwelling cannula. Approximately 425 mL of blood was collected from each subject over the course of the study, including the samples collected for screening and post-study tests
Blood Sample Processing/Storage	Blood samples were centrifuged at 3500 rpm for 8 minutes at approximately 4ºC, within 20 minutes of collection. After being centrifuged, at least 3 mL of the plasma was transferred into 3 labeled polypropylene tubes (3 x at least 1 mL). These tubes were flash frozen as soon as possible after separation. The time at which samples were placed into the solution for flash freezing was recorded. The plasma samples were flash frozen within 20 minutes from the time of sample collection. All samples were stored at -70ºC ± 10ºC or colder pending shipment. The stored samples were then transferred to the analytical facility.
IRB Approval	July 17, 2008
Informed Consent	May 29, 2008
Length of Fasting Before Meal	Subjects fasted for at least 10 hours prior to the start of a high fat, high calorie breakfast and for at least 4 hours following drug administration. Subjects were served a high fat, high calorie breakfast 30 minutes prior to drug administration
Length of Confinement	Subjects were confined to the PMRI clinical facility from at least 34 hours prior to each drug administration until 24 hours post-dose.
Safety Monitoring	Vital signs were not measured throughout the study. Post-clinical laboratory tests for hematology, serum chemistry, and urinalysis and a post-study physical examination (including vital signs measurements), were performed.

Standard FDA Meal Used?	In the fed studies 2008-1807, the FDA standard meal was used.

Comments on Study Design:

The study design is acceptable.

5.1.2.2 Clinical Results

Table 24. Demographics Profile of Subjects Completing the Fed PK Study-Pilot Study

Study No: 2008-1807		
		Treatment Groups
		N = 6
Age (years)	**Mean ± SD** **Range**	33 ± 10 20 - 45
Age Group	**< 18** **18 - 40** **41 - 64** **65 - 75** **> 75**	0 (0.0%) 4 (66.7%) 2 (33.3%) 0 (0.0%) 0 (0.0%)
Sex	**Male** **Female**	1 (16.7%) 5 (83.3%)
Race	**Asian** **Black** **Caucasian** **Hispanic/Latino** **Other**	0 (0.0%) 1 (16.7%) 2 (33.3%) 3 (50.0%) 0 (0.0%)
BMI	**Mean ± SD** **Range**	25.6 ± 2.4 22.8 - 27.9
Other Factors		N/A

Table 25. Dropout Information, Fed PK Study-Pilot Study

No subjects withdrew or were dismissed from study 2008-1807

Table 26. Study Adverse Events, Fed PK Study-Pilot Study

There were no adverse events reported for study 2008-1807.

Table 27. Protocol Deviations, Fed PK Study-Pilot Study

Study No. 2008-1807		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Section 11.12 of the protocol states: "*After being centrifuged, at least 3 mL of the plasma will be transferred into 3 labeled polypropylene tubes (3 x at least 1 mL).*" Less than 1 mL of Subject 03's, Period 1, Draw 19 (24 hour time point) plasma was transferred into the third polypropylene tube. This protocol deviation had no significant impact on the safety of the subject or on the integrity of the study results.	N/A	N/A

5.1.2.3 Bioanalytical Results

Table 28. Assay Validation – Within the Fed PK Study-Pilot Study

Bioequivalence Study No. 2008-1807 Free Eicosapentaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	3.1	6.3	3.6	4.1	3.1	3.5	3.4	1.8	1.3
Inter day Accuracy (%Actual)	102.0	97.0	99.2	97.6	100.3	101.6	101.8	103.4	97.4
Linearity	0.9989-0.9993								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1807 Free Eicosapentaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	400	4000	182	2240	4360
Inter day Precision (%CV)	4.1	2.3	5.1	4.5	4.0	9.2
Inter day Accuracy (%Actual)	96.7	99.8	100.3	96.7	95.0	100.0

Bioequivalence Study No. 2008-1807 Free Docosahexaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	1.1	3.0	5.5	1.2	0.9	8.5	3.6	1.7	1.1
Inter day Accuracy (%Actual)	104.0	92.5	97.2	103.2	100.3	100.9	102.2	102.6	97.7
Linearity	0.9981-0.9996								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1807 Free Docosahexaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	400	4000	707	2070	4190
Inter day Precision (%CV)	4.2	2.7	4.7	4.8	4.5	6.2
Inter day Accuracy (%Actual)	99.0	99.8	98.3	98.2	95.4	100.4

Bioequivalence Study No. 2008-1807 Eicosapentaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	2.7	0.4	3.9	1.0	0.9	3.3	2.9	0.5
Inter day Accuracy (%Actual)	104.0	97.0	101.0	98.8	96.0	106.6	96.4	101.3
Linearity	0.9986-0.9997							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1807 Eicosapentaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (µg/mL)	3.00	20.0	120	6.12	63.1	99.3
Inter day Precision (%CV)	4.0	2.3	3.1	4.5	3.6	3.2
Inter day Accuracy (%Actual)	99.7	97.0	107.5	101.1	101.1	105.7

Bioequivalence Study No. 2008-1807 Docosahexaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	3.6	4.1	0.7	4.6	2.3	2.3	5.1	1.9
Inter day Accuracy (%Actual)	101.0	94.0	103.2	102.0	97.6	105.6	95.5	101.3
Linearity	0.9982-0.9998							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1807 Docosahexaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (µg/mL)	3.00	20.0	120	25.8	56.7	91.9
Inter day Precision (%CV)	1.8	2.6	1.9	2.2	2.2	1.6
Inter day Accuracy (%Actual)	98.0	98.0	107.5	102.7	104.8	109.9

Comments on Study Assay Validation:

The study validation data of the calibrators and quality control samples were not evaluated; the above information is provided for information purposes only.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially; EPA and DHA FFA: 1-3 EPA and DHA total lipids: 4-6

Comments on Chromatograms:

Chromatograms found on page 80 of 767 in the Fed Analytical Report, Protocol No.: 2008-1807 Version: 1, A Single-Dose, Pharmacokinetic Study of Lovaza™ 1000 mg Capsules Under Fed Conditions.

Table 29. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	Repeat Sample Analysis Procedure and Acceptance Criteria

Summary/Conclusions, Study Assays:

The PK study was not evaluated; this information is provided for information purposes only.

5.1.2.4 Pharmacokinetic Results

Table 30. Arithmetic Mean Pharmacokinetic Parameters

Not applicable. The reviewer did not review and reanalyze the BE study data.

Table 31. Geometric Means and 90% Confidence Intervals - Firm Calculated

Lovaza Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Pharmacokinetic Study (Study No. 2008-1807)				
Eicosapentaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	802.36	746.43	107.49	92.83 - 124.47
Cmax	50.41	56.04	89.97	71.05 - 113.92
Docosahexaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	260.64	183.86	141.76	88.45 - 227.22
Cmax	27.54	29.47	93.43	59.98 - 145.55
Eicosapentaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	3.665	4.049	90.53	70.01 - 117.06
Cmax	0.495	0.669	73.98	50.50 - 108.38
Docosahexaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	7.859	8.631	91.05	61.33 - 135.16
Cmax	1.350	1.810	74.54	50.49 - 110.05

Comments on Pharmacokinetic and Statistical Analysis:

Not applicable. The reviewer did not review and reanalyze the BE study data for verification.

Summary/Conclusions, Single-Dose Fed PK Study-Pilot Study:

1. The firm included 6 subjects using the RLD product under fed conditions. The statistical analysis for the PK parameters AUCt and Cmax of plasma free EPA and DHA fatty acids, and total EPA and DHA lipids, after baseline level adjustments as reported by the firm are within the acceptable limits of 80-125%; however, these data were not evaluated by the reviewer.

2. Per the draft guidance, the 90% confidence intervals (CI's) a fed study is based on base line adjusted EPA and DHA ethyl esters. In the Fed Pilot Study Report # 2008-1807, the

firm did not measure the ethyl esters and stated "the active ingredients are the ethyl esters of the EPA and DHA fatty acids. These esters are believed to be completely hydrolyzed in the GI tract and the free fatty acids absorbed. Therefore, in this study, plasma samples were assayed for eicosapentaenoic acid and docosahexaenoic acid from the free fatty acids of plasma and from the plasma total lipids."

3. Per the draft guidance, the baseline-adjusted EPA and DHA total lipids and baseline-adjusted EPA and DHA free fatty acids, and the statistical analysis least squares are to be submitted as supportive evidence.

5.1.3 Single-dose Fed Bioequivalence Study (2008-1835)-Pivotal Study

5.1.3.1 Study Design

Table 32 Study Information

Study Number	2008-1835
Study Title	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters 1000 mg Capsules under Fed Conditions
Clinical Site (Name, Address, Phone #)	Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6 Phone: (416) 759-4111
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP (C)
Dosing Dates	September 12, 2008 and September 19, 2008
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	October 16, 2008 and October 29, 2008 for free eicosapentaenoic acid and October 16, 2008 and October 24, 2008 for free docosahexaenoic acid.
	September 30, 2008 and October 8, 2008 for eicosapentaenoic acid and September 30, 2008 and October 6, 2008 for docosahexaenoic acid.
Analytical Director	(b) (6) M.Sc.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Forty eight (48) days (September 11, 2008 – October 29, 2008) (Free Eicosapentaenoic acid and Free Docosahexaenoic acid) Twenty seven (27) days (September 11, 2008 – October 8, 2008) (Eicosapentaenoic acid and Docosahexaenoic acid)

Table 33. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Omega-3-Acid Ethyl Esters 1000 mg Capsules	Lovaza™ 1000 mg Capsules
Manufacturer	Par Pharmaceutical Companies, Inc.	Catalent Pharma Solutions, USA
Batch/Lot No.	Lot No.: 21680902	Lot No.: 803040W
Manufacture Date	7/17/08	N/A
Expiration Date	N/A	APR 2011
Strength	1000 mg	1000 mg
Dosage Form	Capsules	Capsules
Bio-batch Size	N/A	N/A
Production Batch Size	N/A	N/A
Potency	N/A	N/A
Content Uniformity (min, max, mean)	N/A	N/A
Dose Administered	4 x 1000 mg	4 x 1000 mg
Route of Administration	Oral	Oral

Table 34. Study Design, Single-Dose Fed BE Study-Pivotal Study

Number of Subjects	Period 1: Dosed 80 Period 2: Dosed 71, dropout 04, withdrew 05, Completed and analyzed: 70; Subject 24 withdrew after Pd 2 dosing
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	See Below
Blood Sampling Times	Six pre-dose levels (of EPA and DHA) were measured over a 24-hour interval. All other blood samples were collected prior to drug administration -24 (x2), -23, -22, -21, -20, -19, -18, -17, -16, -15, -14, -12, -10, -8, and -4 hours pre-dose, and within one minute of the scheduled time at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 28, 32, 36, 48, and 72 hours following drug administration in pre-chilled, labeled 06 mL blood collection tubes containing K2EDTA as the anticoagulant.
Blood Volume Collected/Sample	In each period, 37 blood samples from 36 time points were obtained from an arm vein of each subject by direct venipuncture or from an indwelling cannula. Approximately 470 mL of blood was collected from each subject over the course of the study, including the samples collected for screening and post-study tests
Blood Sample Processing/Storage	Blood samples were centrifuged at 3500 rpm for 8 minutes at approximately 4ºC, within 20 minutes of collection. After being centrifuged, Each plasma sample was subdivided into 2 approximately equal aliquots and placed in labeled polypropylene tubes. These tubes were flash frozen as soon as possible after separation. The time at which samples were placed into the solution for flash freezing was recorded. The plasma samples were flash frozen within 20 minutes from the time of sample collection. All samples were stored at -70ºC ± 10ºC or colder pending shipment. The stored samples were then transferred to the analytical facility.
IRB Approval	September 04, 2008
Informed Consent	September 04, 2008
Length of Fasting	Subjects consumed a high fat, high calorie breakfast 24.5 hours and 30 minutes prior to drug administration. Subjects fasted for at least 10 hours prior to the start of each high fat, high calorie breakfast and for at least 4 hours following drug administration.
Length of Confinement	Subjects were confined to the PMRI clinical facility from at least 46 hours prior to each drug administration until at least 36 hours post-dose.
Safety Monitoring	Vital signs were not measured throughout the study. Post-clinical laboratory tests for hematology, serum chemistry, and urinalysis and a post-study physical examination (including vital signs measurements), were performed.

*Randomization Scheme

Subject No.	Subject ID No.	Sequence	Period 1	Period 2
01	(b) (6)	BA	B	A
02		AB	A	B
03		AB	A	B
04		BA	B	-
05		AB	A	B
06		BA	B	A
07		AB	A	B
08		BA	B	A

Subject No.	Subject ID No.	Sequence	Period 1	Period
09	(b) (6)	AB	A	B
10		BA	B	-
11		BA	B	A
12		AB	A	B
13		AB	A	B
14		AB	A	B
15		BA	B	A
16		BA	B	A
17		AB	A	-
18		BA	B	A
19		AB	A	B
20		BA	B	A
22		BA	B	A
23		AB	A	B
24		AB	A	B
25		BA	B	A
26		BA	B	A
27		AB	A	B
28		AB	A	B
29		BA	B	A
30		AB	A	B
31		BA	B	A
32		AB	A	B
33		BA	B	A
34		AB	A	-
35		AB	A	B
36		BA	B	A
39		BA	B	A
40		AB	A	-
41		BA	B	A
42		AB	A	B
43		AB	A	B
44		BA	B	A
45		AB	A	B
46		BA	B	A
47		BA	B	-

Standard FDA Meal Used?	In the fed studies 2008-1835, the FDA standard meal was used.

Comments on Study Design:

The study design is acceptable.

5.1.3.2 Clinical Results

Table 35. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No: 2008-1835		
		Treatment Groups
		N = 70
Age (years)	**Mean ± SD** **Range**	35 ± 9 21 - 53
Age Group	**< 18** **18 - 40** **41 - 64** **65 - 75** **> 75**	0 (0%) 48 (68.6%) 22 (31.4%) 0 (0.0%) 0 (0.0%)
Sex	**Male** **Female**	43 (61.4%) 27 (38.6%)
Race	**Asian** **Black** **Caucasian** **Hispanic/Latino** **Other**	10 (14.3%) 18 (25.7%) 30 (42.9%) 12 (17.1%) 0 (0.0%)
BMI	**Mean ± SD** **Range**	25.3 ± 2.9 19.8 - 29.7
Other Factors		N/A

Table 36. Dropout Information, Fed BE Study-Pivotal Study

Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
04	**Reason:** Personal reasons **Time Dropped-out:** 16:10 **Date Dropped-out:** September 16, 2008 **Treatment:** Reference	1	No	N/A
10	**Reason:** Adverse Events (upset stomach, loose stool) **Time Dropped-out:** 09:30 **Date Dropped-out:** September 22, 2008 **Treatment:** Reference	1	No	N/A
17	**Reason:** Adverse events **Time Dropped-out:** 16:51 **Date Dropped-out:** September 16, 2008 **Treatment:** Test	1	No	N/A
24	**Reason:** Personal reasons **Time Dropped-out:** 11:45 **Date Dropped-out:** September 20, 2008 **Treatment:** Test & Reference	1 and 2	No	N/A

34	**Reason:** Non-compliance **Time Dropped-out:** 15:16 **Date Dropped-out:** September 15, 2008 **Treatment:** Test	1	No	N/A
40	**Reason:** Non-compliance **Time Dropped-out:** 15:16 **Date Dropped-out:** September 15, 2008 **Treatment:** Test	1	No	N/A
47	**Reason:** Personal reasons **Time Dropped-out:** 11:03 **Date Dropped-out:** September 17, 2008 **Treatment:** Reference	1	No	N/A
58	**Reason:** Adverse events (upset stomach, feeling feverish) **Time Dropped-out:** 10:12 **Date Dropped-out:** September 17, 2008 **Treatment:** Test	1	No	N/A
71	**Reason:** Personal reasons **Time Dropped-out:** 16:00 **Date Dropped-out:** September 17, 2008 **Treatment:** Reference	1	No	N/A
73	**Reason:** Adverse events **Time Dropped-out:** 19:24 **Date Dropped-out:** September 13, 2008 **Treatment:** Test	1	No	N/A

Table 37. Study Adverse Events, Fed BE Study-Pivotal Study

System Organ Class Term Preferred Term	**Reported Incidence by Treatment Groups**	
	Fed Bioequivalence Study Study No: 2008-1835	
	Test A N = 76	**Test B** N = 75
Cardiac disorders		
Palpitations	2 (2.6%)	1 (1.3%)
Eye disorders		
Abnormal sensation in eye	0 (0%)	1 (1.3%)
Ocular hyperaemia	2 (2.6%)	0 (0%)
Gastrointestinal disorders		
Diarrhoea	0 (0%)	1 (1.3%)
Dry mouth	1 (1.3%)	0 (0%)
Dyspepsia	2 (2.6%)	4 (5.3%)
Flatulence	1 (1.3%)	1 (1.3%)

System Organ Class Term Preferred Term	**Reported Incidence by Treatment Groups**	
	Fed Bioequivalence Study Study No: 2008-1835	
	Test A N = 76	**Test B** N = 75
Haematochezia	0 (0%)	1 (1.3%)
Nausea	1 (1.3%)	0 (0%)
Stomach discomfort	1 (1.3%)	1 (1.3%)
General disorders and administration site conditions		
Asthenia	1 (1.3%)	0 (0%)
Catheter site haematoma	1 (1.3%)	0 (0%)
Catheter site pain	1 (1.3%)	1 (1.3%)
Catheter site swelling	2 (2.6%)	0 (0%)
Fatigue	1 (1.3%)	0 (0%)
Pyrexia	1 (1.3%)	0 (0%)
Vessel puncture site haematoma	2 (2.6%)	0 (0%)
Vessel puncture site pain	2 (2.6%)	2 (2.7%)
Vessel puncture site reaction	0 (0%)	2 (2.7%)
Infections and infestations		
Folliculitis	1 (1.3%)	0 (0%)
Injury, poisoning and procedural complications		
Contusion	1 (1.3%)	1 (1.3%)
Excoriation	0 (0%)	1 (1.3%)
Investigations		
Alanine aminotransferase increased	2 (2.6%)	0 (0%)
Aspartate aminotransferase increased	3 (3.9%)	1 (1.3%)
Bacteria urine identified	3 (3.9%)	1 (1.3%)
Blood cholesterol increased	2 (2.6%)	2 (2.7%)
Blood creatinine increased	3 (3.9%)	1 (1.3%)
Blood glucose increased	1 (1.3%)	3 (4%)
Blood lactate dehydrogenase increased	1 (1.3%)	1 (1.3%)
Blood triglycerides increased	1 (1.3%)	2 (2.7%)
Blood urea increased	1 (1.3%)	1 (1.3%)
Blood urine present	0 (0%)	1 (1.3%)
Eosinophil count increased	0 (0%)	1 (1.3%)
Haemoglobin decreased	0 (0%)	2 (2.7%)
High density lipoprotein decreased	2 (2.6%)	1 (1.3%)
Lymphocytes count increased	2 (2.6%)	0 (0%)
Red blood cells urine positive	2 (2.6%)	3 (4%)
Urine leukocyte esterase positive	1 (1.3%)	0 (0%)
Very low density lipoprotein increased	1 (1.3%)	2 (2.7%)

System Organ Class Term Preferred Term	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No: 2008-1835	
	Test A N = 76	**Test B** N = 75
White blood cell count increased	1 (1.3%)	0 (0%)
White blood cells urine positive	4 (5.3%)	3 (4%)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (1.3%)	0 (0%)
Back pain	1 (1.3%)	1 (1.3%)
Joint swelling	1 (1.3%)	0 (0%)
Neck pain	1 (1.3%)	0 (0%)
Pain in extremity	2 (2.6%)	1 (1.3%)
Nervous system disorders		
Dizziness	0 (0%)	1 (1.3%)
Dysgeusia	3 (3.9%)	0 (0%)
Headache	6 (7.9%)	7 (9.3%)
Hypoaesthesia	1 (1.3%)	0 (0%)
Somnolence	0 (0%)	1 (1.3%)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	1 (1.3%)	0 (0%)
Pharyngolaryngeal pain	1 (1.3%)	3 (4%)
Rhinorrhoea	2 (2.6%)	1 (1.3%)
Throat irritation	1 (1.3%)	0 (0%)
Skin and subcutaneous tissue disorders		
Generalised erythema	1 (1.3%)	0 (0%)
Vascular disorders		
Hypertension	1 (1.3%)	0 (0%)
Pallor	0 (0%)	1 (1.3%)

Reviewer's Comment:
The severity of all the adverse events was mild.

Table 38. Protocol Deviations, Fed BE Study-Pivotal Study

Study No. 2008-1835		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Only 80 subjects were dosed in Period 1 of the study.	N/A	N/A
The clinic staff inadvertently missed to document the actual collection time of Subject 33's Draw 14 (-8 hour time point), Period 1 blood sample.	N/A	33
Subject 46's Draw 35 (48 hour time point), Period 1 plasma sample was flash frozen 36 minutes after collection, 16 minutes more than the protocol specified. Subject 44's Draw 1 (-24 hour time point), Period 1 plasma sample was flash frozen 26 minutes after collection, 6 minutes more than the protocol specified. Subject 80's Draw 35 (48 hour time point), Period 1 blood sample was centrifuged incorrectly for 10 minutes at 3000 rpm.	80	44, 46
Subjects 43 and 44 were not confined for 46 hours prior to Period 2 drug administration. Subject 43 was confined for 45 hours and 12 minutes and Subject 44 was confined for 44 hours and 33 minutes.	44	43
During Period 1, the temperature of the freezer which stored the plasma samples for Subjects 01-43, were not stored at approximately -70°C.	02, 03, 05, 07, 09, 12, 13, 14, 17, 19, 23, 24, 27, 28, 30, 32, 34, 35, 40, 42, 43	01, 04, 06, 08, 10, 11, 15, 16, 18, 20, 22, 25, 26, 29, 31, 33, 36, 39, 41
Subject 17 took 4 x 200 mg tablets of Advil Regular Strength and 4 tablets of Methocarbamol (400 mg) / Acetyl Salicylic Acid (500 mg) during Period 1, between September 13, 2008 and September 15, 2008. Subject 44 took 4 tablets of Life brand cold relief (30 mg of pseudoephedrine hydrochloride, 15 mg of dextromethorphan hydrobromide and 500 mg of acetaminophen) during Period 1 between September 14, 2008 and September 15, 2008.	17	44

5.1.3.3 Bioanalytical Results

Table 39. Assay Validation – Within the Fed BE Study-Pivotal Study

Bioequivalence Study No. 2008-1835 Free Eicosapentaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	2.3	4.7	4.2	2.5	3.0	2.8	2.4	3.6	2.1
Inter day Accuracy (%Actual)	102.0	96.0	99.0	99.2	100.9	100.9	101.0	102.8	98.0
Linearity	0.9977-0.9999								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1835 Free Eicosapentaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	400	4000	182	2240	4360
Inter day Precision (%CV)	5.3	3.7	3.3	6.0	5.0	4.6
Inter day Accuracy (%Actual)	98.7	101	101	91.8	93.1	94.5

Bioequivalence Study No. 2008-1835 Free Docosahexaenoic Acid									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	10.0	20.0	50.0	125	350	750	1500	3000	5000
Inter day Precision (%CV)	2.8	6.1	4.4	3.2	3.6	2.7	2.6	3.4	1.9
Inter day Accuracy (%Actual)	102.0	97.5	98.0	98.4	101.4	101.3	100.5	102.3	98.3
Linearity	0.9967-0.9999								
Linearity Range (ng/mL)	10.0 -5000 ng/mL								
Sensitivity/LOQ (ng/mL)	10.0 ng/mL								

Bioequivalence Study No. 2008-1835 Free Docosahexaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	400	4000	707	2070	4190
Inter day Precision (%CV)	6.0	4.2	3.3	6.4	5.6	5.1
Inter day Accuracy (%Actual)	97.3	100.5	101.0	94.8	96.4	97.6

Bioequivalence Study No. 2008-1835 Eicosapentaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	5.4	3.2	4.0	4.2	2.8	1.8	2.4	0.9
Inter day Accuracy (%Actual)	100.0	96.0	101.8	103.0	96.4	104.4	96.9	101.3
Linearity	0.9982-0.9999							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1835 Eicosapentaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (µg/mL)	3.00	20.0	120	6.12	63.1	99.3
Inter day Precision (%CV)	4.4	3.9	3.3	4.7	3.8	4.2

Inter day Accuracy (%Actual)	99.3	98.5	104.2	104.6	99.4	102.7

Bioequivalence Study No. 2008-1835 Docosahexaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	6.9	3.1	4.5	4.0	3.2	1.7	3.2	1.3
Inter day Accuracy (%Actual)	100.0	96.5	101.0	104.0	96.4	104.4	96.8	101.3
Linearity	0.9979-0.9999							
Linearity Range (µg/mL)	1.00 -150 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Bioequivalence Study No. 2008-1835 Docosahexaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (µg/mL)	3.00	20.0	120	25.8	56.7	91.9
Inter day Precision (%CV)	4.5	4.1	3.7	4.4	4.5	4.3
Inter day Accuracy (%Actual)	99.0	98.5	104.2	101.6	101.1	104.9

Comments on Study Assay Validation:

The study validation data of the calibrators and quality control samples were not evaluated; the above information is provided for information purposes only.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially; EPA and DHA FFA: 49-64 EPA and DHA total lipids: 28-45

Comments on Chromatograms:

Chromatograms found on page 230 of 6548 in the Fed Analytical Report, Omega-3-acid ethyl esters 1000 mg Capsules, Fed Study
Protocol Number: 2008-1835 Version 1.

Table 40. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	Repeat Sample Analysis Procedure and Acceptance Criteria

Summary/Conclusions, Study Assays:

The PK study was not evaluated; this information is provided for information purposes only.

5.1.3.4 Pharmacokinetic Results

Not applicable. The reviewer did not review and reanalyze the BE study data for verification.

Table 41. Geometric Means and 90% Confidence Intervals - Firm Calculated

Omega-3-Acid Ethyl Esters Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Baseline Adjusted Data				
Fed Bioequivalence Study (Study No. 2008-1835)				
Eicosapentaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	1636.09	1500.30	109.05	102.53 - 115.99
Cmax	73.02	64.50	113.21	106.88 - 119.92
Docosahexaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	760.24	684.71	111.03	103.20 - 119.45
Cmax	45.11	41.90	107.66	100.32 - 115.54

The reviewer located the EPA and DHA FFA PK data in Section 16.1.9 Documentation of Statistical Methods.

Omega-3-Acid Ethyl Esters Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Baseline Adjusted Data				
Fed Bioequivalence Study (Study No. 2008-1835)				
Eicosapentaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	7.320	6.543	111.88	104.24-120.09
Cmax	0.667	0.560	119.13	109.14-130.04
Docosahexaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	19.379	17.961	107.89	96.14-121.08
Cmax	1.700	1.616	105.17	96.60-114.50

Table 42. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Not applicable. The reviewer did not review and reanalyze the BE study data for verification; however, based on the firm's submission, this fed BE study failed the established BE limits of 80-125% for the Cmax parameter of Eicosapentaenoic acid.

Summary and Conclusions, Single-Dose Fed Bioequivalence Study:

1. The statistical analysis for the PK parameters AUCt and Cmax of plasma total EPA and DHA lipids, after baseline level adjustments as reported by the firm are within the acceptable limits of 80-125%; however, these data were not evaluated by the reviewer. The PK parameter Cmax was within the BE limits for the DHA free fatty acid, however, the upper 90% CI limit for EPA free fatty acid was outside the acceptance limit, i.e. [109.14 - 130.04].

2. Per the draft guidance, bioequivalence for a fed study is based on the 90% confidence intervals (CI's) from data of baseline- adjusted EPA and DHA ethyl esters. There were no BE recommendations available for this drug product when the firm submitted this review in November 2008, four years prior to the draft guidance. The firm did not measure the ethyl esters since it stated in the Fed Pilot Study Report # 2008-1807, "the active ingredients are the ethyl esters of the EPA and DHA fatty acids. These esters are believed to be completely hydrolyzed in the GI tract and the free fatty acids absorbed. Therefore, in this study, plasma samples were assayed for eicosapentaenoic acid and docosahexaenoic acid from the free fatty acids of plasma and from the plasma total lipids."

3. Per the draft guidance, the baseline-adjusted EPA and DHA free fatty acids are to be submitted as supportive evidence.

4. The firm's fed BE pivotal study 2008-1835 1) lack the required data for the EPA and DHA ethyl esters, and 2) the supportive data for EPA FFA being outside the limit for the Cmax parameter.

1. The firm's fed BE study 2008-1835 is inadequate.

5.1.4 Single-dose Fed Bioequivalence Study (2011-2545)—Pivotal Study

5.1.4.1 Study Design

Table 43 Study Information

Study Number	2011-2545
Study Title	A Single-Dose, Replicate, Comparative Bioavailability Study of Two Formulations of Omega-3-Acid Ethyl Esters 1000 mg Capsules under Fed Conditions
Clinical Site (Name, Address, Phone #)	Pharma Medica Research Inc., 4770 Sheppard Avenue East, Toronto, Ontario, Canada, M1S 3V6, (416) 759-4111
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Dosing Dates	Period 1: April 23, 2011 Period 2: May 07, 2011 Period 3: May 21, 2011 Period 4: June 04, 2011
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	June 14, 2011 and June 29, 2011 for Total July 04, 2011 and July 20, 2011 for Free
Analytical Director	(b) (6) M.Sc.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Sixty-six (66) days (April 23, 2011 - June 28, 2011) for Total Eighty-seven (87) days (April 23, 2011 - July 19, 2011) for Free

Table 44. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Omega-3 acid ethyl esters 1000 mg Capsules	Lovaza® 1000 mg Capsules
Manufacturer	Par Pharmaceutical, Inc.	Catalent Pharma Solutions for GlaxoSmithKline RTP, USA
Batch/Lot No.	E03110201	1ZP6604
Manufacture Date	03/29/11	N/A
Expiration Date	N/A	OCT2013
Strength	1000 mg	1000 mg
Dosage Form	Capsules	Capsules
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	103.2% (EPA) and 99.7% (DHA)	102.6% (EPA) and 99.7% (DHA)
Content Uniformity (min, max, mean)	102.2%, 103.4%, 102.5% (EPA) 98.9%, 100.0%, 99.2% (DHA)	101.1%, 102.6%, 101.7% (EPA) 98.4%, 99.7%, 98.9% (DHA)
Dose Administered	4 x 1000 mg	4 x 1000 mg
Route of Administration	Oral	Oral

Table 45. Study Design, Single-Dose Fed BE Study-Pivotal Study

Number of Subjects	Period 1: Dosed 48 Period 2: Dosed 45, dropout 01, withdrew 02 Period 3: Dosed 44, withdrew 01 Period 4 Dosed 41, dropout 02 withdrew 01 Completed and analyzed: 41
No. of Sequences	2
No. of Periods	4
No. of Treatments	2 (replicate crossover)
No. of Groups	1
Washout Period	14 days
Randomization Scheme	See below
Blood Sampling Times	Six pre-dose levels (of EPA and DHA) were measured over a 24-hour interval. All other blood samples were collected prior to drug administration and at −24, −16, −10 and 0 hours, and within one minute of the scheduled time at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 28, 32, 36, 48, and 72 hours following drug administration in pre-chilled, labeled 10 mL blood collection tubes containing K2EDTA as the anticoagulant.
Blood Volume Collected/Sample	In each period, 25 blood samples from 24time points were obtained from an arm vein of each subject by direct venipuncture or from an indwelling cannula. Approximately 630 mL of blood was collected from each subject over the course of the study, including the samples collected for screening and post-study tests
Blood Sample Processing/Storage	Blood samples were centrifuged at 3500 rpm for 8 minutes at approximately 4ºC, within 20 minutes of collection. After being centrifuged, at least 3 mL of the plasma was transferred into 3 labeled polypropylene tubes (3 x at least 1 mL). These tubes were flash frozen as soon as possible after separation. The time at which samples were placed into the solution for flash freezing was recorded. The plasma samples were flash frozen within 20 minutes from the time of sample collection. All samples were stored at -70ºC ± 10ºC or colder pending shipment. The stored samples were then transferred to the analytical facility.
IRB Approval	March 03, 2011
Informed Consent	February 10, 2011
Length of Fasting	Subjects consumed a high fat, high calorie breakfast 24.5 hours and 30 minutes prior to drug administration. Subjects fasted for at least 10 hours prior to the start of each high fat, high calorie breakfast and for at least 4 hours following drug administration.
Length of Confinement	Subjects were confined to the PMRI clinical facility from at least 40 hours prior to each drug administration until at least 36 hours post-dose.
Safety Monitoring	Vital signs were not measured throughout the study. Post-clinical laboratory tests for hematology, serum chemistry, and urinalysis and a post-study physical examination (including vital signs measurements), were performed.

Standard FDA Meal Used?	In the fed studies 2011-2545, the FDA standard meal was used.

Randomization Scheme

Subject	Sequence	Period 1	Period 2	Period 3	Period 4
01	BABA	B	A	B	A
02	ABAB	A	B	A	B
03	BABA	B	A	B	A
04	ABAB	A	B	A	B
05	BABA	B	A	B	A
06	ABAB	A	B	A	B
07	BABA	B	A	B	A
08	ABAB	A	B	A	B
09	BABA	B	A	B	A
10	ABAB	A	B	A	B
11	ABAB	A	B	A	B
12	BABA	B	A	B	A
13	BABA	B	A	B	A
14	ABAB	A	B	A	B
15	ABAB	A	B	A	B
16	BABA	B	A	B	A
17	ABAB	A	B	A	B
18	ABAB	A	B	A	B
19	BABA	B	A	B	A
20	BABA	B	A	B	A
21	ABAB	A	B	A	B
22	ABAB	A	B	A	B
23	BABA	B	A	B	A
24	BABA	B	A	B	A
25	ABAB	A	B	A	B
26	ABAB	A	B	A	B
27	BABA	B	A	B	A
28	BABA	B	A	B	A
29	BABA	B	A	B	A
30	ABAB	A	B	A	B

Subject	Sequence	Period 1	Period 2	Period 3	Period 4
31	BABA	B	A	B	A
32	ABAB	A	B	A	B
33	ABAB	A	B	A	B
34	ABAB	A	B	A	B
35	BABA	B	A	B	A
36	BABA	B	A	B	A
37	BABA	B	A	B	A
38	BABA	B	A	B	A
39	ABAB	A	B	A	B
40	ABAB	A	B	A	B
41	BABA	B	A	B	A
42	BABA	B	A	B	A
43	ABAB	A	B	A	B
44	ABAB	A	B	A	B
45	ABAB	A	B	A	B
46	ABAB	A	B	A	B
47	BABA	B	A	B	A
48	BABA	B	A	B	A

Comments on Study Design:

The study design is acceptable.

The subject's were dosed according to the following schedule:
April 23, 2011 (Period 1)
May 07, 2011 (Period 2)
May 21, 2011 (Period 3)
June 04, 2011 (Period 4).

Foods high in omega-3 were restricted from 2 days prior to check-in until the completion of the entire study (e.g. beef, broccoli, Brussel sprouts, cabbage, canola oil, cauliflower, cloves, cod, collard greens, fish, flaxseeds & flaxseed oil, foods fortified with omega-3, green beans, kale, miso, mustard seeds, oregano, rapeseeds & rapeseed oil, raspberries, romaine lettuce, scallops, shrimp, soybeans, spinach, squash, strawberries, tofu, turnip greens, walnuts, and winter squash).

5.1.4.2 Clinical Results

Table 46. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No: 2011-2545		
		N = 45
Age (years)	**Mean ± SD** **Range**	36 ± 11 20 - 55
Age Group	**< 18** **18 - 40** **41 - 64** **65 - 75** **> 75**	0 (0.0%) 27 (60.0%) 18 (40.0%) 0 (0.0%) 0 (0.0%)
Sex	**Male** **Female**	30 (66.7%) 15 (33.3%)
Race	**Asian** **Black** **White** **Hispanic/Latino** **Other**	4 (8.9%) 6 (13.3%) 21 (46.7%) 14 (31.1%) 0 (0.0%)
BMI	**Mean ± SD** **Range**	25.8 ± 2.9 20.0 - 29.6
Other Factors		N/A

Table 47. Dropout Information, Fed Bioequivalence Study

Study No. 2011-2545				
Subject No.	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
05	**Reason:** Adverse events (headache, stomach cramps) **Time Dropped-out:** 10:40 **Date Dropped-out:** May 19, 2011 **Treatment:** Test	2	No	N/A
17	**Reason:** Adverse event (fever) **Time Dropped-out:** 15:36 **Date Dropped-out:** May 05, 2011 **Treatment:** Test	1	No	N/A
22	**Reason:** Noncompliance (positive for cannabinoids (THC)) **Time Dropped-out:** 15:31 **Date Dropped-out:** June 02, 2011 **Treatment:** Test	3	No	N/A
24	**Reason:** Adverse events (nausea, upset stomach) **Time Dropped-out:** 08:15 **Date Dropped-out:** May 07, 2011 **Treatment:** Reference	1	No	N/A

38	**Reason:** Adverse events (infection of eyes) **Time Dropped-out:** 18:45 **Date Dropped-out:** May 05, 2011 **Treatment:** Reference	1	No	N/A
43	**Reason:** Personal **Time Dropped-out:** 19:29 **Date Dropped-out:** May 31, 2011 **Treatment:** Test	3	No	N/A
47	**Reason:** Adverse events (decreased hemoglobin, decreased hematocrit) **Time Dropped-out:** 08:00 **Date Dropped-out:** June 03, 2011 **Treatment:** Reference	3	No	N/A

Table 48. Study Adverse Events, Fed Bioequivalence Study

System Organ Class Term Preferred Term	**Reported Incidence by Treatment Groups**	
	Bioequivalence Study Study No: 2011-2545	
	Test A N = 46	**Test B** N = 47
Cardiac disorders		
Palpitations	1 (2.2%)	0 (0.0%)
Eye disorders		
Eye irritation	1 (2.2%)	2 (4.3%)
Eye pruritus	0 (0.0%)	1 (2.1%)
Ocular hyperaemia	0 (0.0%)	1 (2.1%)
Gastrointestinal disorders		
Abdominal discomfort	0 (0.0%)	1 (2.1%)
Abdominal pain upper	1 (2.2%)	0 (0.0%)
Eructation	1 (2.2%)	0 (0.0%)
Nausea	0 (0.0%)	1 (2.1%)
General disorders and administration site conditions		
Catheter site haematoma	1 (2.2%)	0 (0.0%)
Catheter site pain	1 (2.2%)	0 (0.0%)
Pain	0 (0.0%)	1 (2.1%)
Pyrexia	1 (2.2%)	0 (0.0%)
Infections and infestations		
Eye infection	0 (0.0%)	1 (2.1%)
Injury, poisoning and procedural complications		

System Organ Class Term Preferred Term	**Reported Incidence by Treatment Groups**	
	Bioequivalence Study **Study No: 2011-2545**	
	Test A N = 46	**Test B** N = 47
Scratch	0 (0.0%)	1 (2.1%)
Investigations		
Bacterial test positive	1 (2.2%)	2 (4.3%)
Blood bilirubin	0 (0.0%)	1 (2.1%)
Blood creatinine increased	1 (2.2%)	0 (0.0%)
Blood urine present	1 (2.2%)	1 (2.1%)
Glucose urine	1 (2.2%)	1 (2.1%)
Haematocrit decreased	0 (0.0%)	1 (2.1%)
Haemoglobin decreased	0 (0.0%)	1 (2.1%)
Red blood cells urine positive	0 (0.0%)	1 (2.1%)
Urine leukocyte esterase positive	1 (2.2%)	2 (4.3%)
White blood cells urine positive	1 (2.2%)	2 (4.3%)

System Organ Class Term Preferred Term	Reported Incidence by Treatment Groups	
	Bioequivalence Study Study No: 2011-2545	
	Test A N = 46	Test B N = 47
Nervous system disorders		
Headache	3 (6.5%)	1 (2.1%)
Somnolence	0 (0.0%)	3 (6.4%)
Psychiatric disorders		
Anxiety	1 (2.2%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders		
Rhinorrhoea	0 (0.0%)	1 (2.1%)
Sneezing	0 (0.0%)	1 (2.1%)
Throat irritation	0 (0.0%)	1 (2.1%)
Vascular disorders		
Hypertension	0 (0.0%)	1 (2.1%)

Reviewer's Comment:
The severity of the adverse event is mild or moderate.

Table 49. Protocol Deviations, Fed Bioequivalence Study

Study No. 2011-2545		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
The plasma sample for Subject 37, Period 2, Draw 3, Time Point -10 hours, was not subdivided and remained as one single aliquot.	37	N/A
Subject 02 checked in late and was confined prior to dosing in Period 3 for 39 hours and 38 minutes and not for at least 40 hours prior to dosing.	02	N/A
Plasma samples for Subjects 31-36, Period 3, Draw 13, Time Point 9 hours, were centrifuged for approximately 7 minutes and not for 8 minutes.	32, 33, 34	31, 35, 36

5.1.4.3 Bioanalytical Results

Table 50. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. 2011-2545 Total Eicosapentaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	2.9	1.7	2.2	2.3	2.6	2.2	2.2	0.9
Inter day Accuracy (%Actual)	100.0	101.0	93.4	105.0	102.8	95.8	102.0	99.3
Linearity	0.9982 to 0.9999							
Linearity Range (µg/mL)	1.00 to 150							
Sensitivity/LOQ (µg/mL)	1.00							

Bioequivalence Study No. 2011-2545 Total Eicosapentaenoic Acid							
Parameter	**Quality Control Samples**						
Concentration (µg/mL)	3.00	60.0	120	227	6.54	56.5	117
Inter day Precision (%CV)	3.1	2.2	2.7	4.4	4.8	3.9	4.0
Inter day Accuracy (%Actual)	95.7	100.7	103.3	100.4	95.0	93.6	94.9

Bioequivalence Study No. 2011-2545 Total Docosahexaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	1.00	2.00	5.00	10.0	25.0	50.0	100	150
Inter day Precision (%CV)	3.4	2.0	1.6	2.9	2.1	2.0	1.9	0.7
Inter day Accuracy (%Actual)	100.0	101.5	93.8	105.0	102.0	95.8	102.0	99.3
Linearity	0.9981 to 0.9998							
Linearity Range (µg/mL)	1.00 to 150							
Sensitivity/LOQ (µg/mL)	1.00							

Bioequivalence Study No. 2011-2545 Total Docosahexaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (µg/mL)	3.00	60.0	120	32.0	62.0	122
Inter day Precision (%CV)	2.6	1.9	2.2	3.7	3.3	2.7
Inter day Accuracy (%Actual)	95.7	100.8	102.5	97.8	94.4	94.3

Bioequivalence Study No. 2011-2545 Free Eicosapentaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	10.0	20.0	50.0	100	200	500	1250	2500
Inter day Precision (%CV)	1.8	3.7	3.3	2.5	2.5	1.5	3.2	1.7

Inter day Accuracy (%Actual)	99.9	99.5	100.6	103.0	99.0	96.8	101.8	99.7
Linearity	0.9975 to 0.9998							
Linearity Range (ng/mL)	10.0 to 2500							
Sensitivity/LOQ (ng/mL)	10.0							

Bioequivalence Study No. 2011-2545 Free Eicosapentaenoic Acid						
Parameter	**Quality Control Samples**					
Concentration (ng/mL)	30.0	1000	2000	78.4	878	1880
Inter day Precision (%CV)	5.4	3.3	5.6; 7.2*	4.9	3.4	3.8
Inter day Accuracy (%Actual)	103.0	95.9	101.8; 101.7*	99.7	99.9	95.6

* Value includes the statistical outlier

Bioequivalence Study No. 2011-2545 Free Docosahexaenoic Acid								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	10.0	20.0	50.0	150	400	1000	2500	5000
Inter day Precision (%CV)	1.2	2.6	2.8	1.6	2.6	1.1	3.1	1.6
Inter day Accuracy (%Actual)	99.8	100.5	97.6	106.7	96.5	98.9	98.7	101.0
Linearity	0.9980 to 0.9997							
Linearity Range (ng/mL)	10.0 to 5000							
Sensitivity/LOQ (ng/mL)	10.0							

Bioequivalence Study No. 2011-2545 Free Docosahexaenoic Acid							
Parameter	**Quality Control Samples**						
Concentration (ng/mL)	30.0	2000	4000	7240	243	1840	3740
Inter day Precision (%CV)	5.1	3.5	5.3; 6.9*	4.4	3.0	3.1	3.6
Inter day Accuracy (%Actual)	102.7	97.4	96.4; 96.4*	95.9	100.0	97.8	94.9

* Value includes the statistical outlier

Comments on Study Assay Validation:

The study validation data of the calibrators and quality control samples were not evaluated; the above information is provided for information purposes only.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially; EPA and DHA FFA: 12-23 EPA and DHA total lipids: 12-23

Comments on Chromatograms:

Chromatograms found on page 210 of 5685 in the Fed Analytical Report, Protocol No.: 2011-2545, Analytical Report
Omega-3-acid ethyl esters 1000 mg Capsules, Fed Study, Study Number: 2011-2545.

Table 51. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	REPEAT SAMPLE ANALYSIS PROCEDURE AND ACCEPTANCE CRITERIA

Summary/Conclusions, Study Assays:

The PK study was not evaluated; this information is provided for information purposes only.

5.1.4.4 Pharmacokinetic Results

Table 52. Arithmetic Mean Pharmacokinetic Parameters

Not applicable. The reviewer did not review and reanalyze the BE study data.

Table 53. Geometric Means and 90% Confidence Intervals - Firm Calculated

Eicosapentaenoic Acid from Total Lipids						
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (2011-2545)						
Parameter	*Test*	*Ref*	*Ratio (%)*	*90% C.I.*	*Intra-Sub Within Ref SD (s_{WR})*	*95% Upper Bound for RSABE Criterion*
Cmax	47.61	48.04	99.09	93.45-105.08	0.197	N/A
AUC0-72	N/A	N/A	98.37	N/A	0.378	-0.081717

Eicosapentaenoic Acid from Free Fatty Acids				
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (2011-2545)				
Parameter	*Test*	*Ref*	*Ratio (%)*	*90% C.I.*
Cmax	568.1	585.0	97.12	90.70-103.99
AUC0-72	5320.1	5227.7	101.77	95.93-107.96

Docosahexaenoic Acid from Total Lipids						
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (2011-2545)						
Parameter	*Test*	*Ref*	*Ratio (%)*	*90% C.I.*	*Intra-Sub Within Ref SD (s_{WR})*	*95% Upper Bound for RSABE Criterion*
Cmax	29.54	29.14	101.37	93.99-109.33	0.231	N/A
AUC0-72	N/A	N/A	103.08	N/A	0.339	-0.060883

Docosahexaenoic Acid from Free Fatty Acids						
Dose 4 x 1000 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (2011-2545)						
Parameter	*Test*	*Ref*	*Ratio (%)*	*90% C.I.*	*Intra-Sub Within Ref SD (s_{WR})*	*95% Upper Bound for RSABE Criterion*
Cmax	N/A	N/A	95.79	N/A	0.313	-0.051539
AUC0-72	N/A	N/A	101.71	N/A	0.298	-0.048937

Summary and Conclusions, Single-Dose Fed Bioequivalence Study:

1. The pharmacokinetic measures (AUCt and Cmax) and confidence intervals of AUCt and Cmax for free EPA and DHA fatty acids, and those of total EPA and DHA lipids with baseline-adjustments, as reported by the firm are within the acceptable limits of 80-125%; however, these data were not evaluated by the reviewer.

2. Per the current Draft Guidance for Omega-3 Acid Ethyl Esters Capsules was posted (September 2012), bioequivalence for the fed study is based on the 90% confidence intervals of data from EPA and DHA ethyl esters. There were no BE recommendations available for this drug product when the firm submitted this review in November 2008, four years prior to the draft guidance. In the study report of the failed fed BE study, study 2008-1835, the firm stated "the active ingredients are the ethyl esters of the EPA and DHA fatty acids. These esters are believed to be completely hydrolyzed in the GI tract and the free fatty acids absorbed. Therefore, in this study, **plasma samples were assayed for eicosapentaenoic acid and docosahexaenoic acid from the free fatty acids of plasma and from the plasma total lipids**."

3. The firm's pivotal fed BE study 2011-2545 did not measure the analytes specified in the FDA draft guidance for Omega-3-Acid Ethyl Ester capsule.

4. The firm's fed BE study 2011-2545 is inadequate.

Reviewer's comments:

1. Regarding the above information, the firm acknowledged in its cover letter that its test product formulations for Omega-3 Acid Ethyl Esters Capsules, 1 g, Lot No. E070813[14] (submitted on September 28, 2011) and Lot No. E03110201 (submitted on December 07, 2011) do not meet the recommended criteria for total omega-3-acid ethyl esters and antioxidant established in the Draft Guidance on Omega-3-Acid Ethyl Esters to qualify for the in vitro only option:

    1) The guidance specified that the "Total omega-3 acid ethyl esters should be **NLT 90% (w/w)**", whereas the firm's submitted two formulations do not meet this criteria ((b) (4)% and (b) (4)%);

[14] This lot number is **not** the same as the lot no. used in the firm's fed BE study 2008-1835, i.e. Lot No.: 21680902, submitted on November 10, 2008. On June 07, 2011 the chemistry division requested the firm to submit the quantitative content for its test product provided in its November 10, 2008 submission (DARRTS. 06/07/2011 REV-QUALITY-03(General Review): 06/07/2011 COR-ANDADE-07(Quality Minor Deficiencies). The firm responded on September 28, 2011 with the composition of the seven omega-3 acid ethyl ethers and identified its test product as lot E070813 (DARRTS: 09/28/2011 Quality/Response To Information Request).

2) The guidance specified that the "Alpha-tocopherol should be present in the same concentration as in the RLD' which is 4 mg/g encapsulated oil, whereas the alpha-tocopherol in the firm's submitted two formulations are (b) (4) mg/g respectively.

2. The firm mentioned in its cover letter that "*please note that Par has manufactured an additional batch of the test formulation in 2013 (Batch # E041301) which contains the recommended labeled concentration for total omega-3-acid ethyl esters (i.e., (b) (4) %) and antioxidant, alpha-tocopherol (i.e., (b) (4) mg/g). Batch information and data will be submitted to the ANDA in the August time frame when stability data are available. We have communicated our submission plans to Robert West and Robert Gaines (Regulatory Project Manager) via several email communications. We believe this new information and data will fully address the recommendations outlined in the Agency's September 2012 draft guidance for this product.*"

Following this page, 2 Pages Withheld in Full as (b)(4)

As listed in the table above, the firm's new formulation meet the criterion set for the *in vitro* option in the draft guidance for Omega-3 Acid Esters Capsules. The review of the specifications, method validation and batch analyses for EPA, DHA, sum of EPA and DHA, total Omega-3-Acid Ethyl Esters Content and Alpha-tocopherol is deferred to CMC reviewer.

The firm's formulation is acceptable.

5.3 Dissolution Data and *in vivo* Study Waiver

Dissolution Review Path	DARRTS, ANDA 091018: REV-BIOEQ-02(Dissolution Review), dated 05/04/2009, 02/04/2010, 08/11/2010 and 03/05/2014

5.3.1 Dissolution History

1. There is no USP method for this product. The internal dissolution database recommends a quantitative capsule rupture test (QCRT) for this product as shown in the table below:

Omega-3-Acid Ethyl Esters

Dosage Form: Caspules, Soft Gelatin

Medium: Develop a quantitative rupture test

Apparatus: Develop a quantitative rupture test

Speed/RPMs: Develop a quantitative rupture test

Modify Date: 12/12/2012

Sampling Times:

Volume:

Notes: refer to ANDA 091018 (b) (4) for examples

Specification: Develop a quantitative rupture test

2. In the original submission of 11/10/2008, the firm conducted a disintegration test. With additional information submitted on, the firm's disintegration test was found acceptable by the DBI (DARRTS, ANDA 091018: REV-BIOEQ-02(Dissolution Review), dated 05/04/2009 and 02/04/2010). In addition, the firm developed a QCRT method for its test product following recommendation by DBI. The firm acknowledged the following FDA-recommended QCRT method and specifications (DARRTS, ANDA 091018: REV-BIOEQ-02(Dissolution Review), dated 08/11/2010):

Medium	5% Triton X-100 in water with 1% pancreatin
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	II (paddles)
Rotational Speed	75 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 60 minutes

3. In the November 1, 2013 submission, the firm submitted a different QCRT method on its newly reformulated test product; this method was not the previously reviewed and approved

QCRT method. The firm developed its own method and conducted QCRT with the new method for the *in vivo* study waiver request:

Apparatus:	USP IV, Flow-through Cell
Flow:	2.0 mL/minute
Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specification	The firm did not propose specification.

Additionally, the firm also conducted dissolution testing with a different method for finished product release and proposed specifications for the test drug product:

Medium	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket)
Rotational Speed	100 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in (b) (4) minutes (b) (4)

By comparing the drug release data using flow-through cell and basket in the amendment of 11/01/2013, as well as the data using paddle in the previous amendment, it is found that the methods with flow-through cell and basket, respectively, appear to be more discriminating than the paddle method. The drug release data and variability with flow-through cell and basket are comparable for both EPAee and DHAee. Considering the greater complexity of conducting QCRT using the flow-through cell apparatus, DBI accepts the firm's proposed basket method as the regulatory method for release and stability testing of the test product and recommended specifications of "NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)". (DARRTS, ANDA 091018: REV-BIOEQ-02(Dissolution Review) dated 03/06/2014)

5.3.2 QCRT Testing Results

5.3.2.1 With Flow-through Cell

Dissolution Conditions	**Apparatus:**	USP IV, Flow-through Cell
	Flow:	2.0 mL/minute
	Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL)
	Volume:	900 ml
	Temperature:	37°C ± 0.5°C
Dissolution Testing Site (Name, Address)	Par Pharmaceutical, Inc., One Ram Ridge Road, Spring Valley, NY 10977	

% Released of EPAee

Study Ref No.	Testing Dates	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	45	60	75	90	105	120	150	180	Study Report Location
Study Report #: MV13-063-1	08/19 & 08/21/13	Test Product: Omega-3-Acid Ethyl Esters Lot No. E041301 Date of Manufacture: 01/16/13 Mfr: Par Pharmaceutical Inc.	1 gram Capsule	12	Mean	10	23	35	44	51	57	62	66	72	76	Section 5.3.1.2
					Range										(b) (4)	
					% CV	13	13	11	9	8	7	7	6	6	6	
						Collection Times (minutes) 210	240	300	360	420	480	540	600			
Study Report #: MV13-063-1	08/19 & 08/21/13	Test Product: Omega-3-Acid Ethyl Esters Lot No. E041301 Date of Manufacture: 01/16/13 Mfr: Par Pharmaceutical, Inc.	1 gram Capsule	12	Mean	80	88	89	94	98	99	99	100			
					Range								(b) (4)			
					% CV	6	5	5	4	3	1	1	1			

						Collection Times (minutes)									
						15	30	45	60	75	90	105	120	150	180
Study Report #: MV13-063-1	08/19 & 08/21/13	Reference Product: LOVAZA Capsules Lot No. 1ZP0924 Exp. Date: 02/2014 Mfr: GlaxoSmithKline	1 gram Capsule	12	Mean	7	20	30	38	45	50	55	59	66	71
					Range	(b) (4)									
					% CV	14	13	11	9	8	7	6	6	5	5
						Collection Times (minutes)									
						210	240	300	360	420	480	540	600		
Study Report #: MV13-063-1	08/19 & 08/21/13	Reference Product: LOVAZA Capsules Lot No. 1ZP0924 Exp. Date: 02/2014 Mfr: GlaxoSmithKline	1 gram Capsule	12	Mean	76	80	87	92	95	97	98	98		
					Range	(b) (4)									
					% CV	5	5	5	4	2	1	1	1		

Dissolution Conditions		
	Apparatus:	USP IV, Flow-through Cell
	Flow:	2.0 mL/minute
	Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL)
	Volume:	900 ml
	Temperature:	37°C ± 0.5°C
Dissolution Testing Site (Name, Address)	Par Pharmaceutical, Inc., One Ram Ridge Road, Spring Valley, NY 10977	

% Released of DHAee

Study Ref No.	Testing Dates	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	45	60	75	90	105	120	150	180	Study Report Location
Study Report #: MV13-063-1	08/19 & 08/21/13	Test Product: Omega-3-Acid Ethyl Esters Lot No. E041301* Date of Manufacture: 01/16/13 Mfg: Par Pharmaceutical Inc.	1 gram Capsule	12	Mean	9	22	34	43	51	56	62	66	72	77	Section 5.3.1.2
					Range										(b) (4)	
					% CV	19	13	11	10	8	7	7	6	6	6	
						Collection Times (minutes) 210	240	300	360	420	480	540	600			
Study Report #: MV13-063-1	08/19 & 08/21/13	Test Product: Omega-3-Acid Ethyl Esters Lot No. E041301* Date of Manufacture: 01/16/13 Mfg: Par Pharmaceutical, Inc.	1 gram Capsule	12	Mean	80	84	89	95	99	100	100	101			
					Range								(b) (4)			
					%CV	6	5	5	4	3	2	1	1			

						Collection Times (minutes)									
						15	30	45	60	75	90	105	120	150	180
Study Report #: MV13-063-1	08/19 & 08/21/13	Reference Product: LOVAZA Capsules Lot No. 1ZP0924 Exp. Date: 02/2014 Mfg: GlaxoSmithKline	1 gram Capsule	12	Mean	7	20	30	39	45	51	56	60	67	73
					Range	(b) (4)									
					% CV	14	13	11	10	9	7	7	6	5	5
						Collection Times (minutes)									
						210	240	300	360	420	480	540	600		
Study Report #: MV13-063-1	08/19 & 08/21/13	Reference Product: LOVAZA Capsules Lot No. 1ZP0924 Exp. Date: 02/2014 Mfg: GlaxoSmithKline	1 gram Capsule	12	Mean	78	83	90	96	99	101	102	102		
					Range	(b) (4)									
					%CV	5	5	5	4	3	1	1	1		

5.3.2.2 With Basket

Dissolution Conditions	**Apparatus:**	USP 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120 K/L)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Proposed Specification	Time (minutes) [redacted] (b) (4) Amount Dissolved NLT [redacted] (b) (4) % (Q)	
Dissolution Testing Site	Par Pharmaceutical, Inc One Ram Ridge Road, Spring Valley NY 10977	
Study Report Location	Section 2.7.1.2	

Study Ref. No.	**Testing Date**	**Product ID\ Batch #**	**Dosage Strength & Form**	**No. of Units**		**Time points (minutes)**								
						15	**30**	**60**	**90**	**120**	**180**	**240**	**300**	**360**
						% Released of EPAee								
Study Report #: CS13-044-1	09/25/13	Test Product: Omega-3-Acid Ethyl Esters Capsules, 1g Batch No. E041301 Date of Manufacture:: 01/16/13 Mfr: Par Pharmaceutical, Inc.	1 gram Capsule	12	Mean	7	24	50	68	80	91	94	97	97
					%CV	31.8	18.1	8.0	6.1	6.0	4.8	3.4	2.7	1.9
					High	[redacted] (b) (4)								
					Low									
	09/26/13	Reference Product: LOVAZA Capsules, 1g Lot No. 1ZP0924 Expiration Date: 02/2014 Mfr: GlaxoSmithKline	1 gram Capsule	12	Mean	9	27	53	68	76	84	89	93	95
					%CV	28.6	11.3	5.2	4.0	3.7	3.5	3.1	2.5	2.0
					High	[redacted] (b) (4)								
					Low									

Dissolution Conditions	**Apparatus:**	USP 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120 K/L)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Proposed Specification	Time (minutes) [redacted] (b) (4) Amount Dissolved NLT [redacted] (b) (4) % (Q)	
Dissolution Testing Site	Par Pharmaceutical, Inc One Ram Ridge Road, Spring Valley NY 10977	
Study report Location	Section 2.7.1.2	

Study Ref. No.	**Testing Date**	**Product ID\ Batch #**	**Dosage Strength & Form**	**No. of Units**		**Time points (minutes)**								
						15	**30**	**60**	**90**	**120**	**180**	**240**	**300**	**360**
						% Released of DHAee								
Study Report #: CS13-044-1	09/25/13	Test Product: Omega-3-Acid Ethyl Esters Capsules, 1g Batch No. E041301 Date of Manufacture: 01/16/13 Mfr: Par Pharmaceutical Inc	1 gram Capsule	12	Mean	4	22	48	67	79	92	96	98	100
					%CV	65.5	19.4	8.3	6.7	6.6	6.3	4.8	4.2	3.4
					High	[redacted] (b) (4)								
					Low									
	09/26/13	Reference Product: LOVAZA Capsules, 1g Lot No. 1ZP0924 Expiration Date: 02/2014 Mfr: GlaxoSmithKline	1 gram Capsule	12	Mean	9	26	53	68	77	87	92	96	98
					%CV	34.4	12.1	5.5	4.2	4.0	3.6	3.5	2.9	2.3
					High	[redacted] (b) (4)								
					Low									

5.3.3 Reviewer's Comments

1. The method validation of QCRT with both flow-through cell and basket was found acceptable (DARRTS, ANDA 091018: REV-BIOEQ-02(Dissolution Review) dated 03/06/2014).

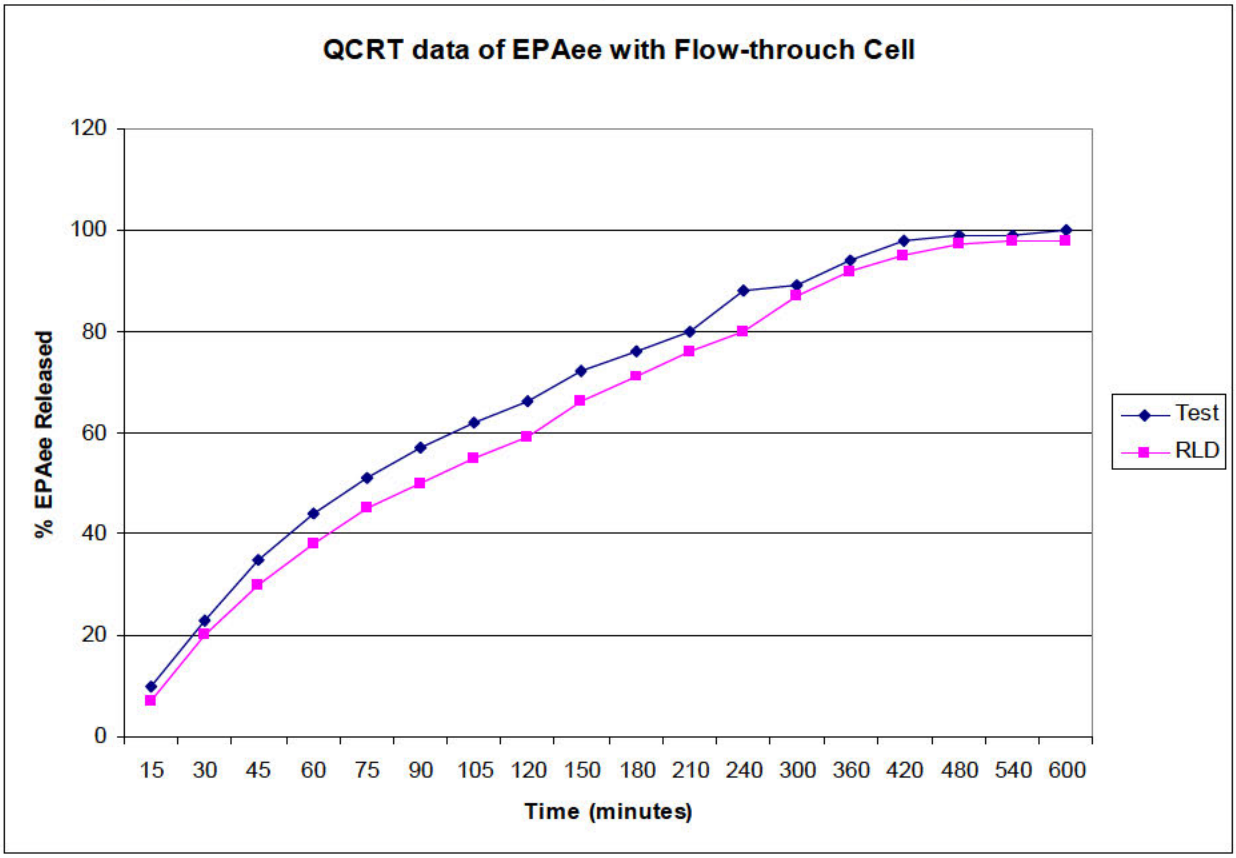
2. Although the QCRT method with basket is recommended for regulatory testing, for BE determination of the test product, the data generated by ***both*** USP apparatuses IV (flow-through cell) and USP I (basket) are evaluated to demonstrate BE in the current review.

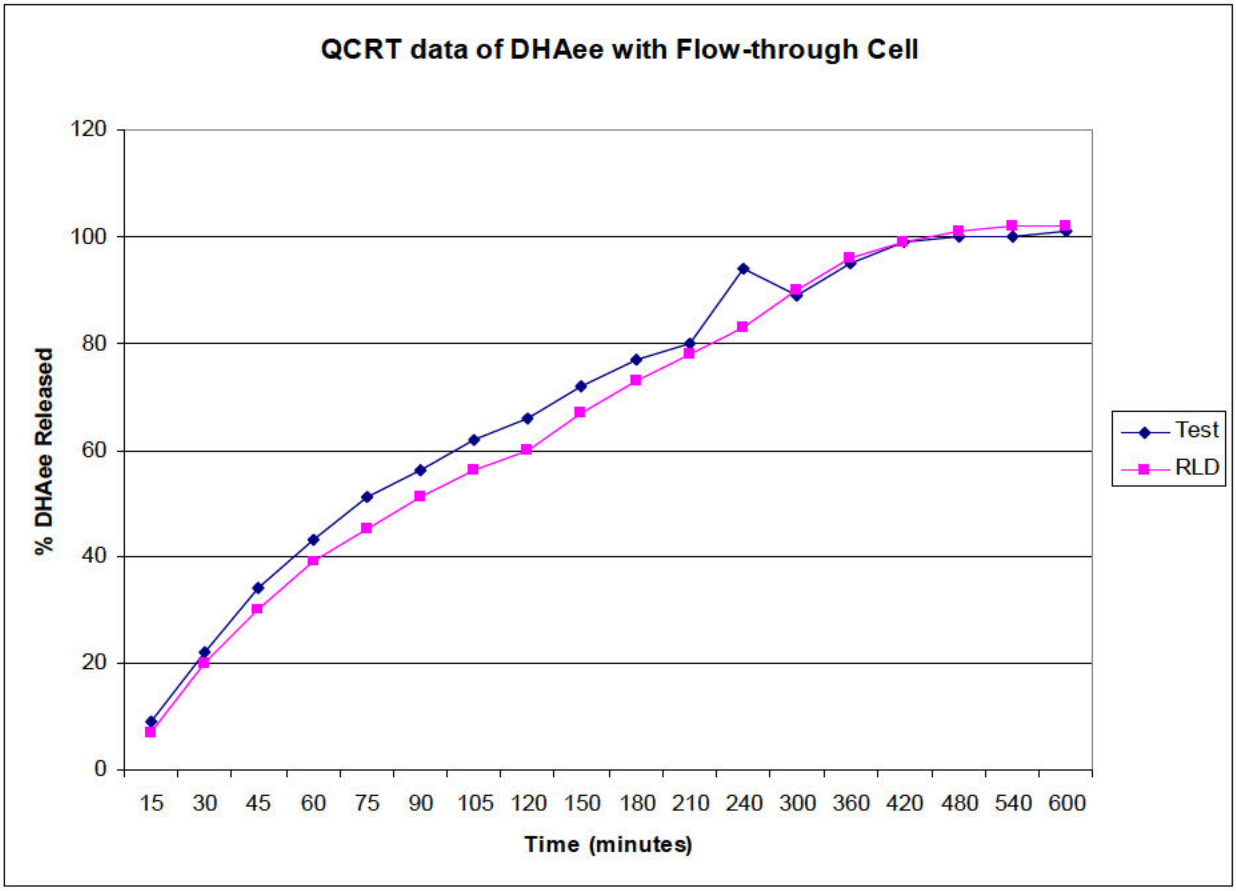
3. The reviewer calculated F2 using both methods and the values are listed in the table below:

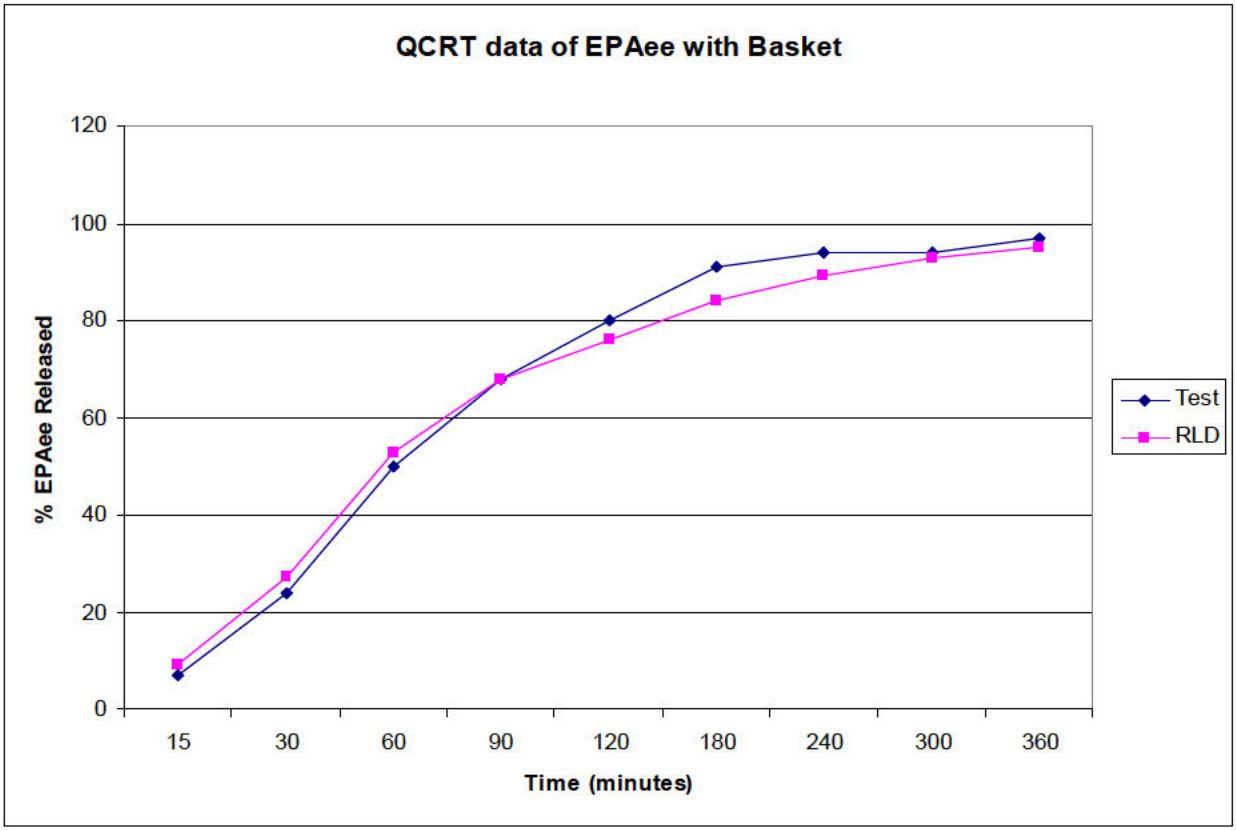
	EPAee	DHAee
Flow-through cell	64.7	68.9
Basket	70.2	69.2

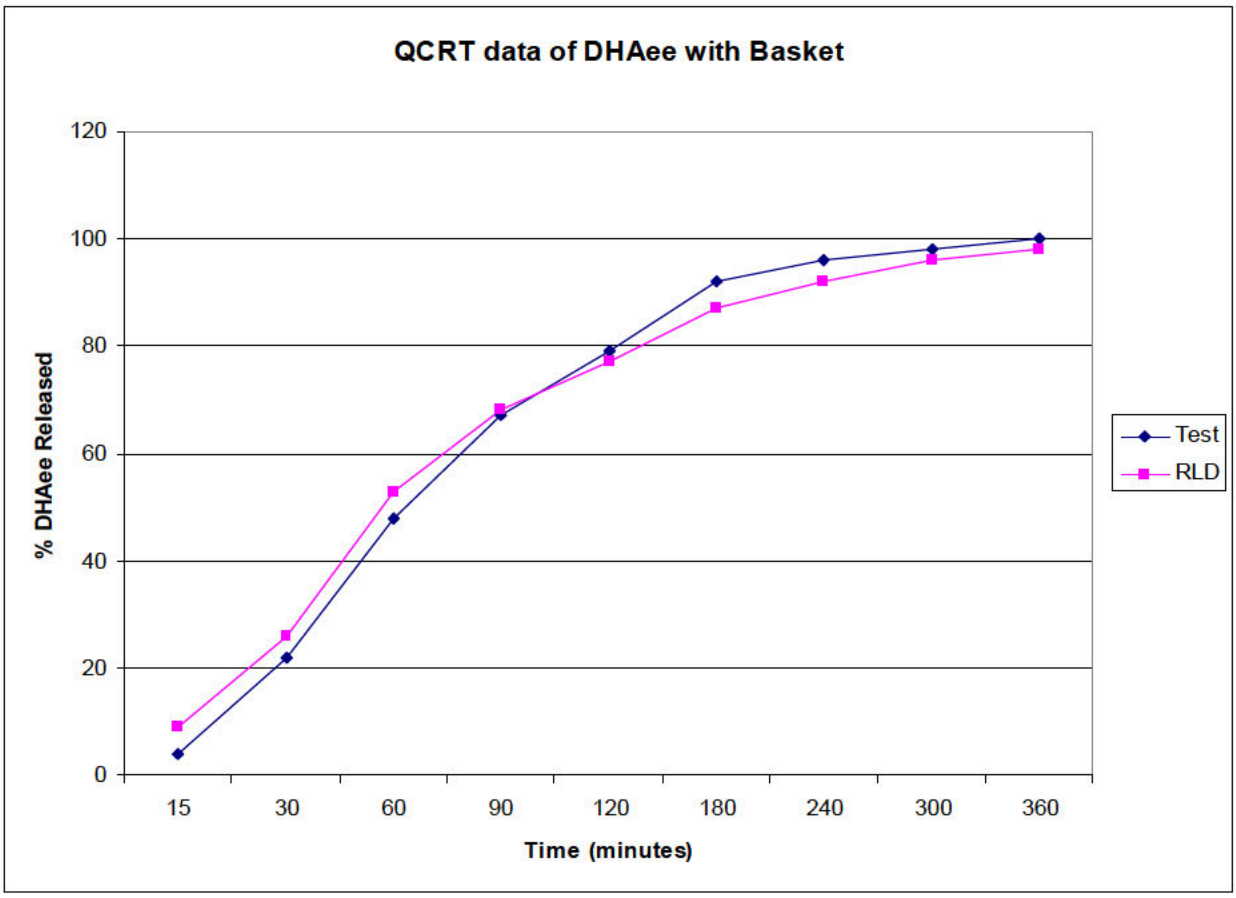
The F2 values for both components using both methods are greater than 50.

4. The QCRT profiles of the test and reference products are depicted in the graphs below:




QCRT data of DHAee with Flow-through Cell
% DHAee Released
120
100
80
60
40
20
0
15 30 45 60 75 90 105 120 150 180 210 240 300 360 420 480 540 600
Time (minutes)
Test
RLD


QCRT data of EPAee with Basket
% EPAee Released
120
100
80
60
40
20
0
15
30
60
90
120
180
240
300
360
Time (minutes)
Test
RLD



The QCRT profiles of DHAee and EPAee using both flow-through cell and basket are comparable between the test and reference products.

5. The firm's *in vivo* study waiver is granted.

6 COMMUNICATION WITH CMC

From: Rahman, Md
Sent: Wednesday, January 22, 2014 2:05 PM
To: Liu, Qing
Cc: Sears, Leigh Ann; Li, Bing; Nguyen, Hoainhon T; Nagavelli, Laxma
Subject: ANDA 091018 Omega-3-Acid Ethyl Ester Capsules

Dear Qing,

Thanks for your query. Since firm's proposed spec at 3.8-4.2mg/g for alpha-tocopherol is tighter than the RLD's spec, it could be considered to pharmaceutical equivalent to the RLD.

Thanks.

Ashiq

From: Liu, Qing
Sent: Wednesday, January 22, 2014 1:38 PM
To: Rahman, Md
Cc: Sears, Leigh Ann; Li, Bing; Nguyen, Hoainhon T
Subject: ANDA 091018 Omega-3-Acid Ethyl Ester Capsules

Dear Md,

I am a reviewer in Division of Bioequivalence I and currently reviewing the bioequivalence portion of ANDA 091018, Omega-3-Acid Ethyl Esters Capsules, 1 gram. I would like your input regarding the formulation.

I have verified each component and found that each excipient of the test formulation meets the criteria (for pharmaceutical equivalence) stated in the Draft Guidance for Omega-3- Acid Ethyl Esters (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320011.pdf), ***except for the antioxidant, alpha-tocopherol*** which I have a question for you.

The Draft Guidance lists the amount of alpha-tocopherol to be 4 mg/g encapsulated oil. The firm submitted the formulation information one lot of its test product and listed the content of alphatocopherol in its formulation as (b) (4) mg/g (see DARRTS: ANDA 091018, Supporting Document #26). The finished product specifications for ANDA 091018, however, list the specification range of 3.8 - 4.2 mg/g for this component, while the finished product specifications for the NDA 21654 (RLD product) list the specification range of (b) (4) mg/g. I am attaching both documents below.

Since the specification range of alpha-tocopherol for ANDA 91018 is within the wider RLD specification range of (b) (4) mg/g, shouldn't the amount of this excipient in the test product be considered the same or equivalent to that of the RLD product. If so, the test formulation should be considered pharmaceutically equivalent to the RLD product, is that correct?

I sincerely appreciate any feedback that you are able to offer.

Qing << File: batch-analyses.pdf >> << File: 3-2-s-4-4-batch-analyses-ANDA091018.pdf >>

BIOEQUIVALENCE COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 091018

APPLICANT: Par Pharmaceuticals Inc.

DRUG PRODUCT: Omega-3 Acid Ethyl Esters Capsules, 1 gram

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

7 OUTCOME PAGE

ANDA: 091018

Enter Review Productivity and Generate Report

Reviewer: Liu, Qing **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: ANDA: Omega-3 Acid Ethyl Esters Capsules, 1 gram

---

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
21407	11/10/2008	Bioequivalence Study (REGULAR)	Fasting Study (2008-1806)	1	1
21407	11/10/2008	Bioequivalence Study (REGULAR)	Fed Study (2008-1807)	1	1
21407	11/10/2008	Bioequivalence Study (REGULAR)	Fed Study (2008-1835)	1	1
21407	12/7/2011	Bioequivalence Study (REGULAR)	Fed Study (2011-2545)	1	1
21407	11/1/2013	Other (REGULAR)	Dissolution-Based Waiver	1	1
21407	9/30/2009	Other (REGULAR)	Study Amendment Without Credit	0	0
21407	5/5/2010	Other (REGULAR)	Study Amendment Without Credit	0	0
21407	8/26/2010	Dissolution Data (REGULAR)	Dissolution Acknowledgement	0	0
21407	6/25/2013	Other (REGULAR)	Study Amendment Without Credit	0	0
				Total:	5

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QING LIU
03/07/2014

BING V LI
03/07/2014

HOAINHON N CARAMENICO
03/07/2014

HOAINHON N CARAMENICO on behalf of DALE P CONNER
03/07/2014

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	091018
Drug Product Name	Omega-3 Acid Ethyl Esters Capsules
Strength (s)	1 g
Applicant Name	Par Pharmaceutical Inc.
Applicant Address	One Ram Ridge Road Spring Valley, New York 10977
US Agent Name and the mailing address	Julie Szozda, Submissions Manager, Regulatory Affairs
US Agent's Telephone Number	845- 573- 5780
US Agent's Fax Number	845- 573- 5795
Original Submission Date(s)	November 10, 2008 September 30, 2009 (dissolution amendment) May 05, 2010 (dissolution amendment) August 26, 2010 (QCRT specifications acknowledgement)
Submission Date(s) of Amendment(s) Under Review	November 01, 2013 (reformulation and *in vitro* testing results) February 18, 2014 (response to ECD letter) February 27, 2014 (response to ECD letter)
First Generic	No
Reviewer	Qing Liu, Ph.D.
OVERALL DISSOLUTION REVIEW RESULT	**INADEQUATE (pending dissolution specification acknowledgement)**

Study Site(s) Information

Study Number (s)	2008-1806	2008-1807	2008-1835	2011-2545
Study Type (s)	Fasting (single-dose study, RLD product only)	Fed (single-dose study, RLD product only)	Fed (single-dose, two-way crossover study using test and RLD product)	Fed (single dose 4-way fully replicated reference-scaled crossover study using test and RLD product)
Strength(s)	4 x 1 g	4 x 1 g	4 x 1 g	4 x 1 g
Clinical Site	Pharma Medica Research Inc.			
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6			
OSI Inspection Status of Clinical Site	**N/A (see comment below)**			
Analytical Site	(b) (4)			
Analytical Address				
OSI Inspection Status of Analytical Site	**N/A (see comment below)**			

Reviewer's Comments: An inspection was requested for the clinical site Pharma Medica Research, Inc., 4770 Sheppard Avenue East, Toronto, Ontario, Canada M1S 3V6 under ANDA (b) (4). The inspection is pending. However, since the firm opted to follow the "*in vitro* option" for evidence of bioequivalence, the inspections for the clinical and analytical sites of the *in vivo* studies are not relevant.

I. EXECUTIVE SUMMARY

This is a dissolution amendment review.

The Division of Bioequivalence I (DBI) previously reviewed the firm's quantitative capsule rupture test (QCRT) and deemed the firm's test method and data acceptable[1]. The firm acknowledged the following FDA recommended method and specifications on August 26, 2010[2].

Medium	5% Triton X-100 in water with 1% pancreatin
Volume	900 mL
Temperature	37°C
USP Apparatus	II (paddles)
Rotational Speed	75 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 60 minutes

In the amendment submitted on 11/01/2013, the firm used a different QCRT method for its newly reformulated test product; this method was not the same as previously reviewed and approved QCRT method. The firm conducted QCRT with the new method for the ***in vivo* study waiver request**:

Apparatus:	USP IV, Flow-through Cell
Flow:	2.0 mL/minute
Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL)
Volume:	900 mL
Temperature:	37°C ± 0.5°C
Specification	The firm did not propose specification.

The firm submitted acceptable method development and method validation reports for the above method.

However, in the same submission, the firm also conducted dissolution testing with a different method for **finished product release testing** and proposed specifications for the test drug product:

[1] DARRTS. Search Terms ANDA 91018 08/11/2010 REV-BIOEQ-02(Dissolution Review)
[2] DARRTS. Search Terms ANDA 91018 08/26/2010 Bioequivalence/Response to Information Request

Medium	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in (b) (4) minutes (b) (4)

The firm submitted acceptable method validation report for the above method.

By comparing the drug release data using flow-through cell and basket in the current amendment, as well as the data using paddle in the previous amendment, it is found that the methods with flow-through cell and basket, respectively, appear to be more discriminating than the paddle method. The drug release data and variability with flow-through cell and basket are comparable for both EPAee and DHAee. Considering the greater complexity of conducting QCRT using the flow-through cell apparatus, DBI accepts the firm's proposed basket method as the regulatory method for release and stability testing of the test product. However, the specification of "NLT (b) (4)% (Q) in (b) (4) minutes" for both EPAee and DHAee proposed by the firm using the basket method is not acceptable. The firm will be asked to acknowledge the following FDA-recommended QCRT method and specification:

Medium	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)

The dissolution testing is **inadequate** pending firm's acknowledgement of FDA-recommended QCRT method and specification.

It should be noted that, although the QCRT method with basket is recommended for regulatory testing, for BE determination of the test product (in a separate BE review document), the data generated by ***both*** USP apparatuses IV (flow-through cell) and USP I (basket) were evaluated and found to demonstrate BE.

II. TABLE CONTENTS

III. DISSOLUTION REVIEW

A. Checklist

Information	YES	NO	N/A
Is there a posted dissolution method on the FDA website?	☒	☐	☐
Did the firm use the above method?	☐	☒	☐
Is there a USP dissolution method?	☐	☒	☐
Did the firm use the USP dissolution method?	☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing?	☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)?	☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method?	☒	☐	☐

B. Additional Information

Method with flow-through cell (apparatus IV):

Dissolution Method #	Not provided.
Deaeration/ degassing of the medium (Yes/No,)	No
Filter Description (if used in dissolution testing)	(b) (4) filter
Sinker Description (if used in dissolution testing)	N/A
Mesh Size Description (if basket used in dissolution testing)	N/A
Sampling (manual/Auto/fiber optics)	Auto
CoA of Test Product (location in the submission)	Module 3.2.P.5.4 (11/01/2013 submission)
CoA of Reference Product (location in the submission)	Module 3.2.P.5.4 (02/18/2014 submission)

Method with basket (apparatus I):

Dissolution Method #	Not provided.
Deaeration/ degassing of the medium (Yes/No,)	No
Filter Description (if used in dissolution testing)	No filter was used.
Sinker Description (if used in dissolution testing)	N/A
Mesh Size Description (if basket used in dissolution testing)	40 (information provided in response to ECD letter #2 on 02/27/2014)
Sampling (manual/Auto/fiber optics)	Information not provided.
CoA of Test Product (location in the submission)	Module 3.2.P.5.4 (11/01/2013 submission)
CoA of Reference Product (location in the submission)	Module 3.2.P.5.4 (02/18/2014 submission)

C. Dissolution Method As Posted on the FDA Website (if any)

Method posted in internal dissolution database: **NOT TO BE RELEASED UNDER FOI**

Omega-3-Acid Ethyl Esters

Dosage Form: Capsules, Soft Gelatin

Medium: Develop a quantitative rupture test

Apparatus: Develop a quantitative rupture test

Speed/RPMs: Develop a quantitative rupture test

Modify Date: 12/12/2012

Sampling Times:

Volume:

Notes: refer to ANDA 091018 (b) (4) for examples

Specification: Develop a quantitative rupture test

D. USP Method (if any)

None

E. Validation of Analytical Method Used in the Dissolution Studies:

1) Method with flow-through cell

HPLC Parameters (if applicable)	
Mobile phase:	(b) (4)
Column:	
Flow rate:	
Detector_RI	
Injection volume:	
Column temperature:	
Run time:	

Analytical Method Validation Report # and Date	(b) (4)
Submission of SOP for Method Validation (Yes/No, Effective Date)	Yes
Address of Method Validation Site	One Ram Ridge Road, Spring Valley, NY 10977
Address of Dissolution Testing Site	Pharmaceutical, Inc., One Ram Ridge Road, Spring Valley, NY 10977
Submission of Dissolution Method Transfer Report (if the dissolution testing site is different from the method validation site) (Yes/No, Location of the Report)	No
Analyte	EPAee and DHAee
Method Description	Apparatus: USP IV, flow-through cell Flow: 2.0 mL/minute Medium: 4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL) Volume: 900 mL Temperature: 37°C ± 0.5°C
Specificity/Placebo interference	No interference of diluent or medium was observed at the working wavelength.
Linearity and Range (unit)	The detector response is linear from 16.75 µg/mL to 871.23 µg/mL for EPAee and 14.02 µg/mL to 728.87 µg/mL (3% to 160% of target concentrations) and square of correlation coefficient is found to be 1.000.
Accuracy/recovery	The individual % recovery ranges from 101.2 to 101.9 (EPAee)% and 101.3% to 101.9% (DHAee)..
Precision	
Repeatability (% RSD)	The % RSD for six QCRT results is found to be 6% (EPAee and DHAee) at (b) (4) minutes.
Intermediate Precision (% RSD)	The difference in the mean % dissolution between precision and intermediate precision was 1% for both components.
Filter Equivalency (% difference)	For standard solutions, (b) (4) (b) (4) are suitable.
Robustness	The method is robust with change in mobile phase, systems, analysts and days.
Standard and Sample Solution Stability	The working standard solution and stock standard solution were stable for 48 hours at room temperature.

2) Method with basket

HPLC Parameters (if applicable)	
Mobile phase:	(b) (4)
Column:	
Flow rate:	
Detector_RI	
Injection volume:	
Column temperature:	
Run time:	

Analytical Method Validation Report # and Date	(b) (4)
Submission of SOP for Method Validation (Yes/No, Effective Date)	Yes
Address of Method Validation Site	One Ram Ridge Road, Spring Valley, NY 10977
Address of Dissolution Testing Site	Pharmaceutical, Inc., One Ram Ridge Road, Spring Valley, NY 10977
Submission of Dissolution Method Transfer Report (if the dissolution testing site is different from the method validation site) (Yes/No, Location of the Report)	No
Analyte	EPAee and DHAee
Method Description	Apparatus: USP (basket) Speed of rotation: 100 rpm Medium: 4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120k/L) Volume: 900 mL Temperature: 37°C ± 0.5°C
Specificity/Placebo interference	No interference of diluent or medium was observed at the working wavelength.
Linearity and Range (unit)	The detector response is linear from 16.75 µg/mL to 871.23 µg/mL for EPAee and 14.02 µg/mL to 728.87 µg/mL (3% to 160% of target concentrations) and square of correlation coefficient is found to be 1.000.
Accuracy/recovery	The individual % recovery ranges from 101.2 to 101.9 (EPAee)% and 101.3% to 101.9% (DHAee).
Precision	
Repeatability (% RSD)	The % RSD for six dissolution results is found to be 1.5% (EPAee) and 2.0 (DHAee) at (b) (4) minutes.
Intermediate Precision (% RSD)	The difference in the mean % dissolution between two analysts was found to be 0% at (b) (4) minutes for EPAee.and 1% for DHAee.
Filter Equivalency (% difference)	N/A (no filter was used)
Robustness	The method is robust with change in mobile phase, systems, analysts and days.
Standard and Sample Solution Stability	The working standard solution and stock standard solution were stable for 48 hours at room temperature.

Reviewer's Comments:

1. The firm provided additional method validation information (validation address, SOPs, filter and accuracy study results) in the response to ECD letter #1 on 02/18/2014.

2. The QCRT methods were validated at Par Pharmaceutical Inc., One Ram Ridge Road, Spring Valley, NY 10977, where QCRT testing was conducted.

3. The QCRT methods validation is acceptable.

F. Summary of In Vitro Dissolution Data

a) QCRT (using Flow-through Cell)

Dissolution Conditions	**Apparatus:**	USP IV, Flow-through Cell
	Flow:	2.0 mL/minute
	Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL)
	Volume:	900 ml
	Temperature:	37°C ± 0.5°C
Dissolution Testing Site (Name, Address)		Par Pharmaceutical, Inc., One Ram Ridge Road, Spring Valley, NY 10977

% Released of EPAee

Study Ref No.	Testing Dates	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	45	60	75	90	105	120	150	180	Study Report Location
Study Report #: MV13-063-1	08/19 & 08/21/13	Test Product: Omega-3-Acid Ethyl Esters Lot No. E041301 Date of Manufacture: 01/16/13 Mfr: Par Pharmaceutical Inc.	1 gram Capsule	12	Mean	10	23	35	44	51	57	62	66	72	76	Section 5.3.1.2
					Range										(b) (4)	
					% CV	13	13	11	9	8	7	7	6	6	6	

						Collection Times (minutes) 210	240	300	360	420	480	540	600		
Study Report #: MV13-063-1	08/19 & 08/21/13	Test Product: Omega-3-Acid Ethyl Esters Lot No. E041301 Date of Manufacture: 01/16/13 Mfr: Par Pharmaceutical, Inc.	1 gram Capsule	12	Mean	80	88	89	94	98	99	99	100		
					Range								(b) (4)		
					% CV	6	5	5	4	3	1	1	1		

						Collection Times (minutes)									
						15	30	45	60	75	90	105	120	150	180
Study Report #: MV13-063-1	08/19 & 08/21/13	Reference Product: LOVAZA Capsules Lot No. 1ZP0924 Exp. Date: 02/2014 Mfr: GlaxoSmithKline	1 gram Capsule	12	Mean	7	20	30	38	45	50	55	59	66	71
					Range										(b) (4)
					% CV	14	13	11	9	8	7	6	6	5	5
						Collection Times (minutes)									
						210	240	300	360	420	480	540	600		
Study Report #: MV13-063-1	08/19 & 08/21/13	Reference Product: LOVAZA Capsules Lot No. 1ZP0924 Exp. Date: 02/2014 Mfr: GlaxoSmithKline	1 gram Capsule	12	Mean	76	80	87	92	95	97	98	98		
					Range								(b) (4)		
					% CV	5	5	5	4	2	1	1	1		

Dissolution Conditions		
	Apparatus:	USP IV, Flow-through Cell
	Flow:	2.0 mL/minute
	Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL)
	Volume:	900 ml
	Temperature:	37°C ± 0.5°C
Dissolution Testing Site (Name, Address)	Par Pharmaceutical, Inc., One Ram Ridge Road, Spring Valley, NY 10977	

% Released of DHAee

Study Ref No.	Testing Dates	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	45	60	75	90	105	120	150	180	Study Report Location
Study Report #: MV13-063-1	08/19 & 08/21/13	Test Product: Omega-3-Acid Ethyl Esters Lot No. E041301* Date of Manufacture: 01/16/13 Mfg: Par Pharmaceutical Inc.	1 gram Capsule	12	Mean	9	22	34	43	51	56	62	66	72	77	Section 5.3.1.2
					Range										(b) (4)	
					% CV	19	13	11	10	8	7	7	6	6	6	
						Collection Times (minutes) 210	240	300	360	420	480	540	600			
Study Report #: MV13-063-1	08/19 & 08/21/13	Test Product: Omega-3-Acid Ethyl Esters Lot No. E041301* Date of Manufacture: 01/16/13 Mfg: Par Pharmaceutical, Inc.	1 gram Capsule	12	Mean	80	84	89	95	99	100	100	101			
					Range								(b) (4)			
					%CV	6	5	5	4	3	2	1	1			

						Collection Times (minutes)									
						15	30	45	60	75	90	105	120	150	180
Study Report #: MV13-063-1	08/19 & 08/21/13	Reference Product: LOVAZA Capsules Lot No. 1ZP0924 Exp. Date: 02/2014 Mfg: GlaxoSmithKline	1 gram Capsule	12	Mean	7	20	30	39	45	51	56	60	67	73
					Range	(b) (4)									
					% CV	14	13	11	10	9	7	7	6	5	5
						Collection Times (minutes)									
						210	240	300	360	420	480	540	600		
Study Report #: MV13-063-1	08/19 & 08/21/13	Reference Product: LOVAZA Capsules Lot No. 1ZP0924 Exp. Date: 02/2014 Mfg: GlaxoSmithKline	1 gram Capsule	12	Mean	78	83	90	96	99	101	102	102		
					Range	(b) (4)									
					%CV	5	5	5	4	3	1	1	1		

b) **Dissolution (using USP 1 Basket)**

Dissolution Conditions	**Apparatus:**	USP 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120 K/L)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Proposed Specification	Time (minutes) [redacted] (b) (4)	Amount Dissolved NLT [redacted] (b) (4) % (Q)
Dissolution Testing Site	Par Pharmaceutical, Inc One Ram Ridge Road, Spring Valley NY 10977	
Study Report Location	Section 2.7.1.2	

Study Ref. No.	**Testing Date**	**Product ID\ Batch #**	**Dosage Strength & Form**	**No. of Units**		**Time points (minutes)**								
						15	**30**	**60**	**90**	**120**	**180**	**240**	**300**	**360**
						% Released of EPAee								
Study Report #: CS13-044-1	09/25/13	Test Product: Omega-3-Acid Ethyl Esters Capsules, 1g Batch No. E041301 Date of Manufacture:: 01/16/13 Mfr: Par Pharmaceutical Inc	1 gram Capsule	12	Mean	7	24	50	68	80	91	94	97	97
					%CV	31.8	18.1	8.0	6.1	6.0	4.8	3.4	2.7	1.9
					High	[redacted] (b) (4)								
					Low									
	09/26/13	Reference Product: LOVAZA Capsules, 1g Lot No. 1ZP0924 Expiration Date: 02/2014 Mfr: GlaxoSmithKline	1 gram Capsule	12	Mean	9	27	53	68	76	84	89	93	95
					%CV	28.6	11.3	5.2	4.0	3.7	3.5	3.1	2.5	2.0
					High	[redacted] (b) (4)								
					Low									

Dissolution Conditions	**Apparatus:**	USP 1 (Basket)
	Speed of Rotation:	100 rpm
	Medium:	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120 K/L)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Proposed Specification	Time (minutes) [redacted] (b) (4)	Amount Dissolved NLT [redacted] (b) (4) % (Q)
Dissolution Testing Site	Par Pharmaceutical, Inc One Ram Ridge Road, Spring Valley NY 10977	
Study report Location	Section 2.7.1.2	

Study Ref. No.	**Testing Date**	**Product ID\ Batch #**	**Dosage Strength & Form**	**No. of Units**		**Time points (minutes)**								
						15	**30**	**60**	**90**	**120**	**180**	**240**	**300**	**360**
						% Released of DHAee								
Study Report #: CS13-044-1	09/25/13	Test Product: Omega-3-Acid Ethyl Esters Capsules, 1g Batch No. E041301 Date of Manufacture: 01/16/13 Mfr: Par Pharmaceutical, Inc.	1 gram Capsule	12	Mean	4	22	48	67	79	92	96	98	100
					%CV	65.5	19.4	8.3	6.7	6.6	6.3	4.8	4.2	3.4
					High	[redacted] (b) (4)								
					Low									
	09/26/13	Reference Product: LOVAZA Capsules, 1g Lot No. 1ZP0924 Expiration Date: 02/2014 Mfr: GlaxoSmithKline	1 gram Capsule	12	Mean	9	26	53	68	77	87	92	96	98
					%CV	34.4	12.1	5.5	4.2	4.0	3.6	3.5	2.9	2.3
					High	[redacted] (b) (4)								
					Low									

Flow-through cell method (for information only):

Dissolution Method SOP effective at the time of testing (Yes/No)	Yes
Were the drug product units pooled during the dissolution testing (Yes/No)?	No
Was the dissolution testing conducted on the bio-batch?	N/A (waiver request, no in vivo study)
Age of the test product at the time of dissolution testing.	7 month
Storage conditions of the test product used in the dissolution testing.	ambient condition
Was the reference product expired at the time of dissolution testing (Yes/No)	No
Comments on the variability of the dissolution data	Acceptable
For two-stage dissolution testing, comment on the method of medium change from acid stage to buffer stage.	N/A

Basket method:

Dissolution Method SOP effective at the time of testing (Yes/No)	No (effective at 10/29/2013)
Were the drug product units pooled during the dissolution testing (Yes/No)?	No
Was the dissolution testing conducted on the bio-batch?	N/A (waiver request, no in vivo study)
Age of the test product at the time of dissolution testing.	8 month
Storage conditions of the test product used in the dissolution testing.	ambient condition
Was the reference product expired at the time of dissolution testing (Yes/No)	No
Comments on the variability of the dissolution data	Acceptable
For two-stage dissolution testing, comment on the method of medium change from acid stage to buffer stage.	N/A

Reviewer's Comment:

The firm provided storage condition for the test product and SOP effective date in the response to ECD #1 on 02/18/2014.

G. Reviewer's Comments for Dissolution Testing

1. The firm did not submit data using the QCRT method that was accepted earlier (paddle). It is not clear why the firm developed new QCRT method for the newly formulated test product.

2. In the firm's method development report, it did not include the optimization of the method using basket as apparatus. Per USP PF Charter 35(4), for Lipid-filled Gelatin Capsules, baskets may not be suitable in certain instances. (b) (4)

In the firm's amendment dated 09/30/2009, the firm had the following statements: *'the first actual dissolution using a* (b) (4) ***All further experiments were run using Apparatus 2, paddles and helix sinkers****'*. In the amendment submitted 02/18/2014 (firm's response to ECD letter #1), the firm provided the following justification of using basket: "*The statements from Par's QCR amendment submitted on 09/30/2009 (Report* (b) (4) *) were based on observations made during dissolution testing with medium containing a significant amount, up to* (b) (4) *. Subsequent to the issuance of the Draft Guidance on Omega-3-Acid Ethyl Esters (September 2012) Par undertook development of a Quantitative Capsule Rupture (QCR) test using USP Apparatus 4 based on this guidance. During development it was noted that a laminar medium flow is very important in obtaining reproducible results with adequate precision. Thus, Par developed and optimized the procedure for analysis of samples of Omega-3-Acid Ethyl Esters Capsules, 1 gram on the rate of drug release using USP Apparatus IV with medium containing 4.0% Triton X-100, a surfactant, in 0.01N HCl with pepsin (120000 ± 5% Units/1L) . This procedure was used to establish in-vitro bioequivalence between Par and RLD product. Based on the data obtained for QCR testing, it was decided to maintain the same dissolution medium for finished product release and stability analysis using USP Apparatus I baskets in order to align both procedures. It is observed that soft gelatin capsules do not clog the basket's mesh in this aqueous media, and the USP Apparatus 1 with baskets ensure laminar medium flow.*"

The firm indicated that with the medium of 4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120000 ± 5% units per 1000 mL), the soft gelatin capsules did not clog the basket.

3. The QCRT methods used for in-house ANDAs are listed in the table below:

ANDA	Firm	Current DB Status	Dissolution Method	Reference
091028	Teva	Eligible for in vitro study option.	DB recommends the firm develop QCRT using the following method: 900 mL, 1%, 2%, 5%, 8%, 10% etc. of labrasol in HCl using paddle @ 50, 75 or 100 rpm.	GONG, LI 12/14/2012 N/A 12/14/2012 REV-BIOEQ-01(General Review)

091018	Par	Currently under review	On 8/26/2010, the firm acknowledged the following dissolution method and specification for the proposed test product: Medium: 900 mL of 5% Triton X-100 in water with 1% pancreatin Apparatus: USP II (Paddle) Speed: 75 rpm Specification: NLT (b)(4)% (Q) of labeled amount of EPA and DHA in 60 minutes.	DARRTS, ANDA 091018, Firms Submission #16, 08/26/2010 Bioequivalence/Response to Information Request.
090973	Apotex	No bio review of full ANDA is conducted.	The firm is asked to provide method development report for QCRT. Firm's method use (b)(4) paddle with sinker at (b)(4) rpm	GONG, LI 10/28/2013 N/A 10/28/2013 REV-BIOEQ-02(Dissolution Review)
(b)(4)				
204940	Amneal	No bio review	No Review	
(b)(4)				

As shown in the above table, based on the dissolution method development from ANDAs for the same drug product, Triton X-100 and labrasol are suitable surfactant used in the QCRT; and USP apparatus II (paddle) is a suitable apparatus for the test.

4. The data comparisons of the firm's accepted method (paddle) and newly proposed methods (Basket and Apparatus IV) are shown in the following table:

Testing Date	Method	Lot#	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	150 min	180 min	210 min	240 min
EPA: mean % (CV%)														
3/26/2010	Paddle@75 rpm, 900 mL of 5% Triton X-100 in water with 1% Pancreatin (earlier approved method)	T: #216809	50.4 (36.7)	76.4 (16.8)	89.4 (8.9)	95.1 (5.3%)	-	-	-	-	-	-	-	
3/31/2010		R: #803040	42.2 (29.5)	71.4 (12.9)	87.3 (5.4)	94.5 (2.4)	-	-	-	-	-	-	-	
9/25/2013	Basket@100 rpm, 900 mL of 4% Triton X-100 in 0.01 N HCl with pepsin (120K/L) (newly developed method)	T: #E41301	7 (31.8)	24 (18.1)	-	50 (8.0)	-	68 (6.1)	-	80 (6.0)	-	91 (4.8)	-	94 (3.4)
9/26/2013		R: #1ZP0924	9 (28.6)	27 (11.3)	-	53 (5.2)	-	68 (4.0)	-	76 (3.7)	-	84 (3.7)	-	89 (3.1)
8/19/2013	Apparatus IV, 2mL/min, 4% Triton X-100 in 0.01 N HCl with pepsin (120K/L) (newly developed method)	T: #E41301	10 (13)	23 (13)	35 (11)	44 (9)	51 (8)	57 (7)	62 (7)	66 (60	72 (6)	76 (6)	80 (6)	88 (5)
8/19/2013		R: #1ZP0924	7 (14)	20 (13)	30 (11)	38 (9)	45 (8)	50 (7)	55 (6)	59 (6)	66 (5)	71 (5)	76 (5)	80 (5)

Testing Date	Method	Lot#	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	150 min	180 min	210 min	240 min
DHA: mean % (CV%)														
3/26/2010	Paddle@75 rpm, 900 mL of 5% Triton X-100 in water with 1% Pancreatin	T: #216809	54 (37)	81 (17)	96 (9)	103 (5)	-	-	-	-	-	-	-	-
3/31/2010		R: #803040	45 (31)	77 (13)	94 (6)	103 (3)	-	-	-	-	-	-	-	-
9/25/2013	Basket@100 rpm, 900 mL of 4% Triton X-100 in 0.01 N HCl with pepsin (120K/L)	T: #E41301	4 (66)	22 (19)	-	48 (8)	-	67 (7)	-	79 (7)	-	92 (6)	-	96 (5)
9/26/2013		R: #1ZP092 4	9 (34)	26 (12)	-	53 (6)	-	68 (4)	-	77 (4)	-	87 (4)	-	92 (4)
8/19/2013	Apparatus IV, 2mL/min, 4% Triton X-100 in 0.01 N HCl with pepsin (120K/L)	T: #E41301	9 (19)	22 (13)	34 (11)	43 (10)	51 (8)	56 (7)	62 (7)	66 (6)	72 (6)	77 (6)	80 (6)	84 (5)
8/19/2013		R: #1ZP092 4	7 (14)	20 (13)	30 (11)	39 (10)	45 (9)	51 (7)	56 (7)	60 (6)	67 (5)	73 (5)	78 (5)	83 (5)
*													(b) (4)	

The method with flow-through cell and basket appear to be more discriminating than the paddle method for both EPAee and DHAee.

4. QCRT data at the final time points of the test product with basket and flow through cells are shown in the table below:

EPAee:

	180 min	240 min	300 min	360 min
Basket: Mean (Range)	91 (b) (4)	94 (b) (4)	97 (b) (4)	97 (b) (4)
Basket: CV%	4.8	3.4	2.7	1.9
Flow-through cell: Mean (Range)	76 (b) (4)	88 (b) (4)	89 (b) (4)	94 (b) (4)
Flow-through cell: CV%	6	5	5	4

DHAee:

	180 min	240 min	300 min	360 min
Basket: Mean (Range)	92 (b) (4) (b) (4)	96 (b) (4)	98 (b) (4)	100 (b) (4)
Basket: CV%	6.3	4.8	4.2	3.4
Flow-through cell: Mean (Range)	77 (b) (4)	84 (b) (4)	89 (b) (4)	95 (b) (4)
Flow-through cell: CV%	6	5	5	4

5. The QCRT data using flow-through cell and basket for the test and reference products are shown in the graphs below:

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The drug release data with flow-through cell and basket are comparable for both EPAee and DHAee. The variability of the drug release data using both methods is acceptable. Due to the greater complexity of conducting the flow-through cell QCRT testing, the basket method will be recommended to the firm as regulatory method for release and stability testing of the test product. The specifications of "NLT (b) (4)% (Q) in (b) (4) minutes" for both EPAee and DHAee proposed by the firm using the basket method are not acceptable. The firm will be asked to acknowledge the following FDA-recommended QCRT method and specifications:

Medium	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)

H. Deficiency Comments for Dissolution Testing

Based on the QCRT data submitted by the firm, the following method is recommended to the firm as regulatory method for release and stability testing of the test product. The firm will be asked to acknowledge the following FDA-recommended QCRT method and specification:

Medium	4.0% Triton X-100 in 0.01 *N* HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)

I. Dissolution Recommendations

The *in vitro* dissolution testing conducted by Par Pharmaceutical Inc. on its test product, Omega-3-acid ethyl esters Capsules, 1 g, lot # E041301, comparing it to Smithkline Beecham's Lovaza® Capsules, 1 g, lot # 1ZP0924, is **inadequate due to the deficiencies cited above.**

The firm should be informed of the above deficiencies and recommendation.

IV. OSI INSPECTION STATUS

N/A (The firm opted for *in vivo* study waiver option.)

V. Attachment

A. Dissolution Focal Point Comments Focal Point Comments Regarding the Firm's Proposed Dissolution Testing Method

From: Zhang, Hongling
Sent: Wednesday, November 13, 2013 11:13 AM
To: Williams, Zakia R
Cc: Li, Bing; Liu, Qing
Subject: RE: ANDA 091018

Hi Zakia,

Please see the attached document for the response of your consult. I also attached the review of science team for the BE recommendations of this drug product.

Please let me know if you have any questions.

Please consult with your TL and DBI managements for the final decision.

Thanks,

Hongling << File: consult-ANDA 91018-Zakia.doc >> << File: Omega-3-acid ethyl esters cap 21654.doc >>

_____ Hi Zakia,

In the ECD letter dated 6/12/2013, the DB asked the firm to provide concentrations for all ingredients (API and inactive ingredients) in the test formulation, not to reformulate the test product.
The firm submitted the original application on 11/10/2008 which included two pilot BE studies under fasting and fed conditions, respectively and one pivotal BE study under fed condition. The DB posted the Draft BE Guidance in September, 2012 and recommended 2 options to demonstrate the bioequivalence: in vitro option with Quantitative Capsule Rupture Test and in vivo option with fasting and fed BE studies. If the firm chooses in vitro option, the test product should meet all the API pharmaceutical equivalence requirements and is equivalent to the RLD product in containing alpha-tocopherol at a concentration of 4 mg/g.
In the current amendment (dated 11/1/2013), to address the requirements outlined in the draft guidance, the firm manufactured an additional batch (#E041301) in April 2013. The firm selected the in vitro option and requested for waiver of in-vivo studies based on in-vitro study. The firm re-developed the Quantitative Capsule Rupture Test (QCRT) as recommended in the draft BE guidance. Per the draft BE guidance, the firm should develop the in vitro drug release method using USP Apparatus 4 (flow-through cell). A second method using USP Apparatus 2 (paddle) may be developed in conjunction with the method using USP Apparatus 4 for comparison, if desired.
The firm did not state whether the formulation and manufacture process of this new submission batch (#E041301) are different from the previously submitted bio batch (lot #216809, manufactured on 7/17/2008). The firm submitted the CMC information for the current batch in module 3. I suggest you check with the chemistry reviewer first to confirm that the firm's test

product is considered pharmaceutically equivalent to the RLD product as required in the draft BE guidance, so that the test product is eligible for the in vitro option. This step was also done for (b) (4) ANDA 091028 for the same drug product.

ANDA History of Omega-3 Acid Ethyl Ester Capsules:

To date, the OGD has received (b) (4) ANDA applications for Omega-3 Acid Ethyl Ester Capsules. The status of these ANDA is summarized in the following table:

ANDA	Firm	Current DB Status	Dissolution Method	Reference
091028	Teva	Eligible for in vitro study option.	DB recommends the firm develop QCRT using the following method: 900 mL, 1%, 2%, 5%, 8%, 10% etc. of labrasol in HCl using paddle @ 50, 75 or 100 rpm.	GONG, LI 12/14/2012 N/A 12/14/2012 REV-BIOEQ-01(General Review)
091018	Par	Currently under review	On 8/26/2010, the firm acknowledged the following dissolution method and specification for the proposed test product: Medium: 900 mL of 5% Triton X-100 in water with 1% pancreatin Apparatus: USP II (Paddle) Speed: 75 rpm Specification: NLT (b) (4) % (Q) of labeled amount of EPA and DHA in 60 minutes.	DARRTS, ANDA 091018, Firms Submission #16, 08/26/2010 Bioequivalence/Response to Information Request.
090973	Apotex	No bio review of full ANDA is conducted.	The firm is asked to provide method development report for QCRT. Firm's method use (b) (4) paddle with sinker at (b) (4) rpm	GONG, LI 10/28/2013 N/A 10/28/2013 REV-BIOEQ-02(Dissolution Review)
(b) (4)				

(b) (4)

204940	Amneal	No bio review	No Review	

(b) (4)

As shown in the above table, based on the dissolution method development from ANDAs for the same drug product, Triton X-100 and labrasol are suitable surfactant used in the QCRT; and USP apparatus II (paddle) is a suitable apparatus for the test.

Firm's Method Development Report:

In the method development report, the firm had the following statements: (b) (4)

The firm's method development included the following tests:

Dissolution Condition	Lot # and No. of units	Observations	Data Interpretation/Conclusion
(b) (4)			

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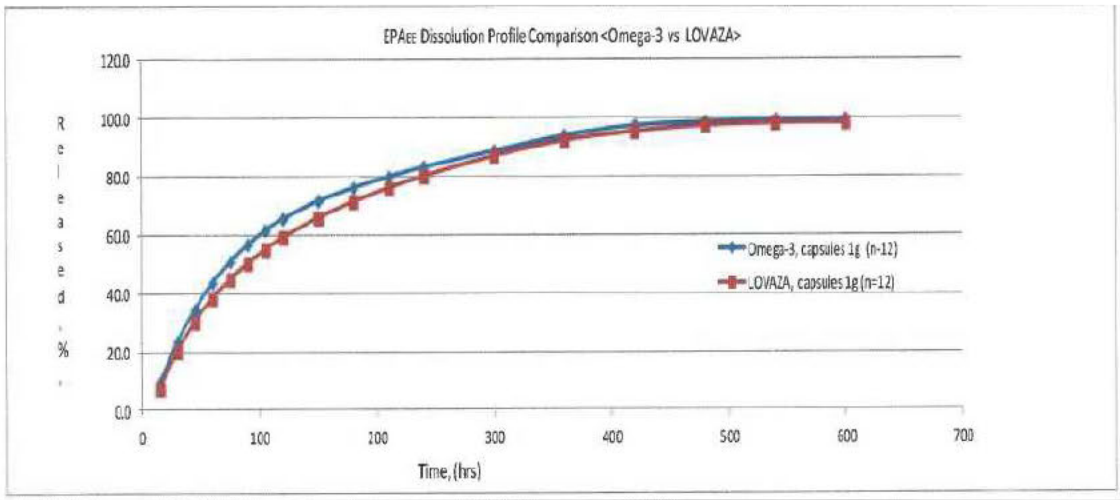
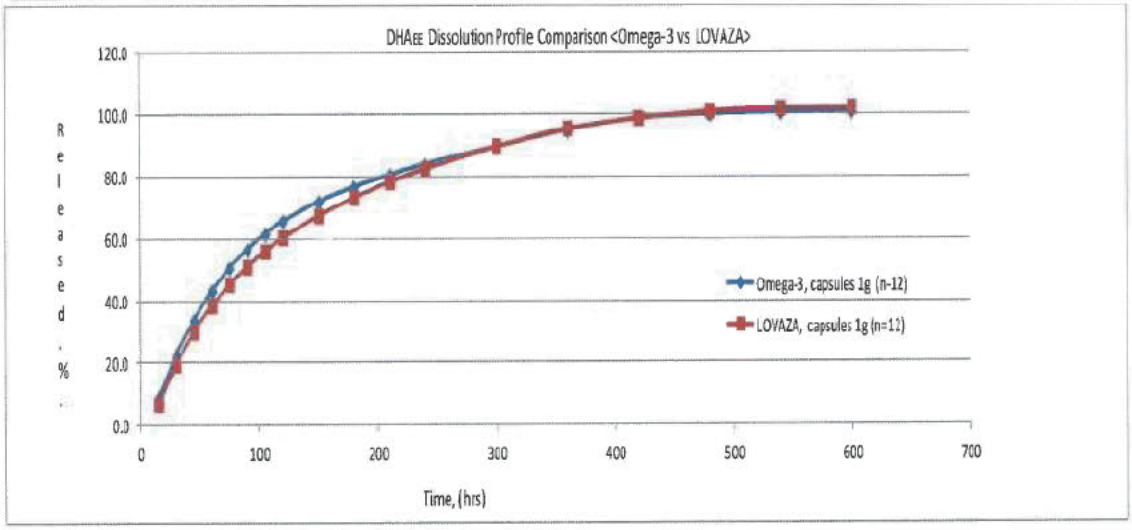
(b) (4)

Finalized Method:
Apparatus: USP apparatus IV, flow-through cell (closed system)
Medium: 4.0% Triton X-100 in 0.01 N HCl with pepsin (120000 ± 5% Units per 1000 mL)
Flow: 2.0 mL/min
Temperature: 370C ± 0.5 0C
Volume: 900 mL
Glass Beads: (b) (4) mm diameter, (b) (4) g
Filter: (b) (4)
Sample Volume: 1.2 mL
Dissolution Time Points/Intervals: (b) (4)

In vitro BE Study:

The firm's proposed QCRT method was validated and the firm conducted the comparative QCRT for the test (lot # E041301) and reference product (lot #1ZP0924). The results showed that the dissolution profile of the test product is comparable to the reference product, shown in the following figure:





In addition to this method, the firm also conducted the comparative QCRT using USP I (basket) at 100 rpm and the same medium (900 mL of 4.0% Triton X-100 in 0.01 N HCl with pepsin (120 K/L) and proposed NLT (b) (4)(Q) in (b) (4)hours as specification. In the firm's method development report, it did not include the optimization of the method using basket as apparatus. Per USP PF Charter 35(4), for Lipid-filled Gelatin Capsules, baskets may not be suitable in certain instances. (b) (4) In the firm's amendment dated 09/30/2009, the firm had the following statements: *'the first actual dissolution using a mixture of* (b) (4) ***All further experiments were run using Apparatus 2, paddles and helix sinkers'***. The firm should provide the justification for using basket as the apparatus for the QCRT.

Per the draft BE guidance, *'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 (paddle) may be developed in conjunction with the method using USP Apparatus 4 for comparison, if desired. The data from USP Apparatus 4, and from USP Apparatus 2 (if conducted), should be submitted to the Division of Bioequivalence for evaluation and for determination of the most suitable method'*.

There are three dissolution-only reviews for the application. Based on the firm's method development conducted on the bio batch, the DB recommended the following method and specifications for the proposed test product:

Medium: 900 mL of 5% Triton X-100 in water with 1% pancreatin
Apparatus: USP II (Paddle)
Speed: 75 rpm
Specification: NLT (b)(4)% (Q) of labeled amount of EPA and DHA in 60 minutes

On 8/26/2010, the firm acknowledged the above dissolution method and specifications. The data comparisons of the firm's accepted method and newly proposed method are shown in the following table:

Testing Date	Method	Lot#	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	150 min	180 min	210 min	240 min
EPA: mean % (CV%)														
3/26/2010	paddle@75 rpm, 900 mL of 5% Triton X-100 in water with 1% Pancreatin	T: #216809	50.4 (36.7)	76.4 (16.8)	89.4 (8.9)	95.1 (5.3%)	-	-	-	-	-	-	-	
3/31/2010		R: #803040	42.2 (29.5)	71.4 (12.9)	87.3 (5.4)	94.5 (2.4)	-	-	-	-	-	-	-	
9/25/2013	Basket@100 rpm, 900 mL of 4% Triton X-100 in 0.01 N HCl with pepsin (120K/L)	T: #E41301	7 (31.8)	24 (18.1)	-	50 (8.0)	-	68 (6.1)	-	80 (6.0)	-	91 (4.8)	-	94 (3.4)
9/26/2013		R: #1ZP0924	9 (28.6)	27 (11.3)	-	53 (5.2)	-	68 (4.0)	-	76 (3.7)	-	84 (3.7)	-	89 (3.1)
8/19/2013	Apparatus IV, 2mL/min, 4% Triton X-100 in 0.01 N HCl with pepsin (120K/L)	T: #E41301	10 (13)	23 (13)	35 (11)	44 (9)	51 (8)	57 (7)	62 (7)	66 (60	72 (6)	76 (6)	80 (6)	88 (5)
8/19/2013		R: #1ZP0924	7 (14)	20 (13)	30 (11)	38 (9)	45 (8)	50 (7)	55 (6)	59 (6)	66 (5)	71 (5)	76 (5)	80 (5)

Testing Date	Method	Lot#	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	150 min	180 min	210 min	240 min
DHA: mean % (CV%)														
3/26/2010	paddle@75 rpm, 900 mL	T: #216809	54 (37)	81 (17)	96 (9)	103 (5)	-	-	-	-	-	-	-	-

3/31/2010	of 5% Triton X-100 in water with 1% Pancreatin	R: #803040	45 (31)	77 (13)	94 (6)	103 (3)	-	-	-	-	-	-	-	-
9/25/2013	Basket@100 rpm, 900 mL of 4% Triton X-100 in 0.01 N HCl with pepsin (120K/L)	T: #E41301	4 (66)	22 (19)	-	48 (8)	-	67 (7)	-	79 (7)	-	92 (6)	-	96 (5)
9/26/2013		R: #1ZP0924	9 (34)	26 (12)	-	53 (6)	-	68 (4)	-	77 (4)	-	87 (4)	-	92 (4)
8/19/2013	Apparatus IV, 2mL/min, 4% Triton X-100 in 0.01 N HCl with pepsin (120K/L)	T: #E41301	9 (19)	22 (13)	34 (11)	43 (10)	51 (8)	56 (7)	62 (7)	66 (6)	72 (6)	77 (6)	80 (6)	84 (5)
8/19/2013		R: #1ZP0924	7 (14)	20 (13)	30 (11)	39 (10)	45 (9)	51 (7)	56 (7)	60 (6)	67 (5)	73 (5)	78 (5)	83 (5)

As shown in the above table, the DB previously recommended method using Paddle as apparatus provided over (b)(4)% drug release in (b)(4) minutes, while the methods proposed in the current amendment provided only (b)(4)% drug release in (b)(4) minutes. In my opinion, the firm's QCRT submitted in current amendment is incomplete. We should ask the firm to provide:

1. Comparative QCRT using the firm previously accepted method (using paddle) on the new submission batch (#E041301) and unexpired RLD product.

2. Justifications of using basket as the apparatus for the QCRT since in the amendment dated 09/30/2009, the firm stated that (b)(4)

From: Williams, Zakia R
Sent: Friday, November 08, 2013 5:07 PM
To: Zhang, Hongling
Cc: Li, Bing; Liu, Qing
Subject: ANDA 091018

Good Afternoon Hongling,

I am reviewing the dissolution data for ANDA 091018, Omega-3 Acid Ethyl Esters Capsules, 1 g.

The firm developed its own quantitative capsule rupture tests (QCRT) (Method 1 and Method II) and submitted it to the DB for review back in 2010 . The DB reviewer evaluated the firm's proposed methods and accepted the firm's Method I: 900 mL of 5% Triton X-100 in water with 1% pancreatin using USP Apparatus 2 (paddle) at 75 rpm. The DB asked the firm to acknowledge the following dissolution method and specification for its test product :

Medium 5% Triton X-100 in water with 1% pancreatic
Volume 900 mol
Temperature 37°C
SUP Apparatus II (paddles)
Rotational Speed 75 rpm
Specification NOT (b)(4)% (Q) of labeled amount of each EPA and DHAL in the dosage form is dissolved in 60 minutes

At that time, there was no Draft Guidance for this test product. In a recent ECD to the firm regarding its formulation, we asked the firm to reformulate its test product (if they preferred to submit a waiver and pursue the in vitro option) conduct additional QCRT testing data on its newly re-formulated test product.

On November 1, 2013, the firm submitted its new formulation and additional QCRT testing data for the new manufactured test lot, Omega-3 Acid Ethyl Esters Capsules, 1 g, Lot No. 251302. Instead of using the previously approved FDA method, the firm developed a different method per the Draft Guidance on Omega-3 Acid Ethyl Esters.

Apparatus: USP IV, Flow-through Cell
Flow: 2.0 mL/minute
Medium: 4.0% Triton X-100 in 0.01 N HCl with pepsin (120000 ± 5% units per 1000 mL)
Volume: 900 Ml
Temperature: 37°C ± 0.5°C
Specification NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in (b)(4) minutes

Can you please evaluate the firm's newly developed method (and proposed specification) and provided me with adequate recommendation for the firm.

For ease for your review << File: QCRT mv report 110113.pdf >> << File: bio-sum-tables 110113.docx >> , I have attached the firm's summary tables, and the method development and optimization report.

Zakia R. Williams, Ph.D.

Pharmacologist
Reviewer Team #4
FDA/CDER/OPS/OGD/DBE
PH 240-276-8801
Fax 240-276-8766
zakia.williams@fda.hhs.gov

B. Easily Correctible Deficiency (ECD) Letter #1

Date: 2/03/2014

ANDA#: 091018

Firm: Par Pharmaceuticals Inc.

Drug product: Omega-3 Acid Ethyl Esters Capsules, 1 gram

Contact: Julie Szozda, Submissions Manager, Regulatory Affairs

Reviewer: Qing Liu

Re: Quantitative Capsule Rupture (QCR) testing study reports

1. According to the amendment dated 11/01/2013, you chose QCR method using basket for finished drug release. In your QCR amendment dated 09/30/2009, you had the following statements: *'the first actual dissolution using a* (b) (4) ***All further experiments were run using Apparatus 2, paddles and helix sinkers'***. Please explain your latest proposal of using basket in the QCR testing in relation to the earlier statements above about the inappropriateness of the basket. Please provide supporting data with your response.

2. You did not provide the Certificate of Analysis (CoA) for the reference listed drug product, Smithkline Beecham's Lovaza® Capsules, lot #IZP0924, used in the QCR testing with flow-through and basket methods. Please submit the information.

3. You did not provide storage conditions of the test (lot # E041301) and reference (lot #1ZP0924) products used in the QCR testing with flow-through and basket methods (i.e., how the test lots were stored between the manufacturing date and testing date; similarly, how the reference lots were stored following acquisition). Please provide the storage conditions for the products used in the QCR testing.

4. For the validation of the assay method used in the QCR testing with basket, you did not submit the method Standard Operation Procedure (SOP) or method validation SOP. Please provide the relevant SOPs.

5. Your QCR testing using the basket method was conducted at Par Pharmaceutical Inc., One Ram Ridge Road, Spring Valley, NY 10977. You did not provide the detailed address (street number, street name, city, state and country) where the method validation of the QCR testing was performed in the method validation report (reports # (b) (4)). Please provide this information. The suitability of the QCR testing method should be validated at the same site where QCR testing is conducted. Therefore, if the method validation site is different from the QCR testing site, you should either validate the QCR method at the QCR testing site or provide the method transfer report between sites.

6. In your QCR testing validation report using the basket method (reports # (b) (4), located at Module 3.2.P.5.3), you did not conduct accuracy or intermediate precision studies. Please provide results for these studies.

7. For the validation of the assay method used in the QCR testing with flow-through cell, you did not submit the method SOP or method validation SOP. Please provide the relevant SOPs.

8. Your QCR testing using the flow-through cell was conducted at Par Pharmaceutical Inc., One Ram Ridge Road, Spring Valley, NY 10977. You did not provide the detailed address (street number, street name, city, state and country) where the method validation of the QCR testing was performed in the method validation report (reports # (b) (4)). Please provide this information. The suitability of the QCR testing method should be validated at the same site where QCR testing is conducted. Therefore, if the method validation site is different from the QCR testing site, you should either validate the QCR method at the QCR testing site or provide the method transfer report between sites.

9. In your QCR validation report using the flow-through cell method (reports # (b) (4), located at Module 3.2.P.5.3), you did not conduct accuracy study. In addition, you used (b) (4) (b) (4) filter in the QCR testing but did not conduct filter validation study. Please provide results for these studies.

C. Easily Correctible Deficiency (ECD) Letter #2

Date: 2/26/2014

ANDA#: 091018

Firm: Par Pharmaceuticals Inc.

Drug product: Omega-3 Acid Ethyl Esters Capsules, 1 gram

Contact: Julie Szozda, Submissions Manager, Regulatory Affairs

Reviewer: Qing Liu

Re: Quantitative Capsule Rupture (QCR) testing method

For your proposed QCRT method with basket, you did not specify the mesh size for the basket. If you did not use the USP 40-mesh basket, please provide justification for not using the USP mesh size, and full description of the mesh basket used in your proposed method for evaluation.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT (PROCESSED BY BIO-PM)

ANDA: 091018

APPLICANT: Par Pharmaceuticals Inc.

DRUG PRODUCT: Omega-3 Acid Ethyl Esters Capsules, 1 gram

The Division of Bioequivalence I (DBI) has completed its review of the drug release testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver request will be conducted later. The following deficiency has been identified:

1. Your quantitative capsule rupture testing (QCRT) data, using the method stated below, are acceptable. However, your proposed specifications of "NLT (b) (4)% (Q) in (b) (4) minutes" for both DHAee and EPAee are not acceptable. Based on the submitted data, DBI recommends the following QCRT method and specifications for release and stability testing of your test product:

Medium	4.0% Triton X-100 in 0.01 N HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)

The following comment is for future submissions of QCRT:

2. Your Finished Product/Stability Analytical Procedure SOP # (b) (4) for the above QCRT was effective 10/29/2013, while the QCR testing was conducted in 09/2013. In future submissions, please be advised that an effective SOP should be in place prior to conducting the QCRT.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA: 091018

Enter Review Productivity and Generate Report

Completed Assignment for 091018 ID: 21622

Reviewer: Liu, Qing **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Dissolution Amendment: Omega-3 Acid Ethyl Esters Capsules, 1 gram

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
21622	11/1/2013	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
				Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QING LIU
03/04/2014

BING V LI
03/05/2014

HOAINHON N CARAMENICO
03/06/2014

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW-2ND
DISSOLUTION AMENDMENT

ANDA No.	091018		
Drug Product Name	Omega-3 Acid Ethyl Esters Capsules		
Strength(s)	1 g		
Applicant Name	Par Pharmaceutical Inc.		
Address	One Ram Ridge Road Spring Valley, New York 10977		
Applicant's Point of Contact	Julie Szozda		
Contact's Telephone Number	845- 573- 5780		
Contact's Fax Number	845- 573- 5795		
Original Submission Date(s)	November 10, 2008 September 30, 2009		
Submission Date(s) of Amendment(s) Under Review	May 5, 2010		
Reviewer	Ke Ren. Ph.D.		
Study Number (s)	2008-1806	2008-1807	2008-1835
Study Type (s)	Fasting (single-dose study, RLD drug only)	Fed (single-dose study, RLD drug only)	Fed (single-dose, two-way crossover study)
Strength (s)	4 x 1 g	4 x 1 g	4 x 1 g
Clinical Site	Pharma Medica Research Inc.		
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6		
Analytical Site	(b) (4)		
Analytical Site Address			
Overall Review Result	**INADEQUATE pending the firm's acceptance to FDA-recommended dissolution method and specification**		
Bioequivalence Study Tracking/supporting Document#	**Study / Test Type**	**Strength**	**Review Result**
12	Dissolution	1 g	**INADEQUATE**

I. Executive Summary

This ANDA is referencing NDA 021654 for Lovaza® from SmithKline Beecham. There is a "dissolution only" review and a dissolution amendment review on this ANDA 091018.

Par Pharmaceutical Inc.'s submitted its response to the deficiency comments made by the Division of Bioequivalence (DBE) in its letter dated May 5, 2010. As per the dissolution

amendment review the DBE requested the firm to conduct additional dissolution testing to develop an appropriate quantitative rupture test method. In this 2nd dissolution amendment the firm has provided the additional dissolution data per DBE's requests.

In the current development report, the firm investigated using water with different concentrations of Triton X-100 (5%, 8% and 10%) as the dissolution medium, and with USP Apparatus 2 (paddle) at different agitation speeds (50 rpm, 75 rpm and 100 rpm). Based on the dissolution data the firm submitted, these methods are associated with various drawbacks indicating that they are not appropriate quantitative rupture test method for this drug product (refer to Reviewer's Comments for details). In addition, the firm also investigated the dissolution testing using 5% Triton X-100 in water with 1% pancreatin as the dissolution medium at different agitation speeds (50 rpm, 75 rpm and 100 rpm).

The reviewer combined the dissolution data from 1st dissolution amendment and current submission using water with different concentrations of Triton X-100 as the dissolution medium. All the dissolution testing was done on **unexpired biolots** (T and R). In the 1st amendment the test biolot #21680902 was 11 to 13 months old. In the 2nd amendment the test biolot #21680902 was 20 months old. The following are the 7 sets of dissolution testing the firm submitted using Apparatus 2 (paddle).

1. (b) (4)
2.
3.
4. 5% Triton X-100 at 50, 75 and 100 rpms
5. 8% Triton X-100 at 50, 75 and 100 rpms
6. 10% Triton X-100 at 50, 75 and 100 rpms
7. 5% Triton X-100 + 1% pancreatin at 50, 75 and100 rpms

This reviewer rejected those dissolution conditions wher (b) (4) only the 7 set was eligible for consideration. The % dissolution at 60 minutes of the 7 set is shown below.

DRUG	RPM	Mean % EPA	Range EPA	Mean % DHA	Range DHA
TEST	50	81.4	(b) (4)	86.1	(b) (4)
RLD	50	77.7		84.4	
TEST	**75**	95.1		102.6	
RLD	**75**	94.5		102.8	
TEST	100	95.3		104.1	
RLD	100	97.1		106.8	

At the 100 rpm, the test product in the above table demonstrated very rapid dissolution at early time points (e.g., at 15 min, (b) (4) % was dissolved for EPA and (b) (4) % was

dissolved for DHA). Based on the dissolution data above the reviewer recommends the following method and specification which the test drug product will meet at the S1 level.

Medium: Water + 5% Triton X-100 with 1% pancreatin
Apparatus; USP apparatus 2 (paddle)
Speed: 75 rpm
Volume: 900 mL
Specification: NLT (b)(4)% (Q) of EPA and DHA is dissolved in 60 minutes.

(Note: The 2 tier dissolution testing was not recommended (b) (4)

In this amendment the firm proposed two methods. Those are:

Method 1:
900 mL of 5% Triton X-100 in water with 1% pancreatin using USP Apparatus 2 (paddle) at 75 rpm. Specification: NLT (b)(4)% (Q) of each EPA and DHA is dissolved in 60 minutes.
Method 2:
(b) (4)

The Method 1 is identical to the method recommended by this reviewer but the specification is different (b) (4) and more appropriate. The DBE requests the firm to accept and acknowledges the method 1 with (b) (4) specification.

The DBE has requested a new site inspection from Division of Scientific Investigations (DSI) for the clinical site. The analytical site was last inspected in (b) (4) and outcome was (b) (4)

The DBE will review the fasted and fed BE studies at a later date.

The dissolution testing is **incomplete.**

II. Background

- The firm submitted its original application on November 10, 2008. The firm claimed that it conducted a disintegration test per USP <711>. The DBE had done a "dissolution only" review on this ANDA **[DARRTS for 091018 Ren, Ke 05/04/2009 N/A 05/04/2009 REV-BIOEQ-02 (Dissolution Review) Archive].** There are 3 deficiencies regarding lack of detailed information for the disintegration test, long term stability data and quantitative rupture test. DBE communicated those three deficiencies to the firm on May 06, 2009 **[DARRTS**

for 091018 Chun, Nam J, 05/06/2009 Mail 05/06/2009 COR-ANDADE-01 (Bio Incomplete Deficiencies) Archive].

- On September 30, 2009, the firm submitted its response to the above mentioned 3 deficiencies comments made by the DBE in its letter of May 6, 2009. The DBE reviewed this submission (1st amendment) [**DARRTS for 091018 Ren, Ke 02/04/2010 N/A 02/04/2010 REV-BIOEQ-02 (Dissolution Review) Archive]** and found 2 deficiencies. The firm provided the acceptable long term stability data, detailed information for the disintegration test. However, the firm had not yet developed an appropriate quantitative rupture test method for the test product. DBE recommended the firm to conduct further investigation: 1) repeat the comparative quantitative capsule rupture test with **various** (b) (4) Triton X-100 concentrations and at various (b) (4) **agitation** speeds; and 2) encourage to develop different test conditions refer to reference *USP PF Charter 35 (4) Stimuli to the Revision Process: Liquid-filled Gelatin Capsules.* The DBE communicated those two deficiencies to the firm on February 17, 2010 [**DARRTS for 091018 Chun, Nam J, 02/17/2010 Fax 02/17/2010 COR-ANDADE-01 (Bio Incomplete Deficiencies) Archive].** The current submission provides a response to those two deficiencies and is reviewed in this document.

III. Table of Contents

IV. Drug Product Information, PK/PD Information, and Relevant DBE History:

DARRTS 091018 Ren, Ke 05/04/2009 N/A 05/04/2009 REV-BIOEQ-02 (Dissolution Review) Archive

DARRTS 091018 Ren, Ke 02/04/2010 N/A 02/04/2010 REV-BIOEQ-02 (Dissolution Review) Archive

V. Review of Submission:

The two deficiencies, firm's answers and the reviewer's evaluations of those answers are shown below.

DEFICIENCY COMMENT #1 and 2*: As requested, you have explored different in vitro testing conditions in developing a quantitative rupture test method for the test*

product. Your method development report demonstrated that testing in (b) (4) *media with the surfactants of* (b) (4) *On the other hand, the results of your testing in the aqueous media with different concentrations of the surfactant Triton X-100 has shown to be more promising.* (b) (4)

1. *Therefore, the DBE recommends that you further modify the testing method with the aqueous media of Triton X-100 to achieve more gradual rupture and dispersion process, using* (b) (4) *concentrations of Triton X-100 concentrations and/or* (b) (4) *agitation speeds, as suggested below:*

   Medium: *Water + (5% Triton X-100, or 8% Triton X-100, or 10% Triton X-100)*
   Apparatus: *USP apparatus II (paddle)*
   Speed: *50 rpm, or 75 rpm, or 100 rpm*
   Volume: *900 mL*
   Sampling: *Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media*

   If necessary, you may try varying the media volume.

2. *Alternatively, you may consider using USP Apparatus IV (flow-through Cell) or USP Apparatus III (reciprocating cylinder) instead of Apparatus II (paddle) to avoid practical problems such as the oil floating to the surface of the medium and concentrating around the shaft. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. Please refer to the reference article, USP PF Charter 35 (4) Stimuli to the Revision Process: Liquid-filled Gelatin Capsules for helpful considerations in developing an in vitro testing method for similar dosage forms. As advised in this article, a quantitative capsule rupture test characterizes the capsule shell rupture process as well as the dispersion of the active ingredient in the surrounding medium, and thus is a more appropriate way to describe the drug releasing process from its formulation. The DBE currently recommend quantitative capsule rupture test be performed for all soft gel capsule products in which the Active Pharmaceutical Ingredient (API) is dissolved in an oily matrix*

FIRM'S RESPONSES: *In accordance with the Agency's recommendation, several media using Triton X-100 in water at different concentrations and at different rpm were*

evaluated. All experiments were carried out using Apparatus 2, paddle and 900 mL of a medium. To prevent floating of the capsules, helix sinkers were used. Since the results obtained from the first six capsules demonstrated high variability at 60 minutes, the experiments were discontinued. Results of these experiments are provided in the below report in an abbreviated format, i.e. average, max and min values and %RSD.

Alternatively, an attempt to employ USP Apparatus III was made [redacted] (b) (4)

Based on the data provided in the Dissolution Method Development Report, Report # [redacted] (b) (4) *, it can be concluded that dissolution of Omega-3-Acid Ethyl Esters Capsules can be carried out using 5% solution of Triton X-100 in water containing 1% of pancreatin as medium.*

Par proposes the following two methods for the Agency's consideration:

- *900 mL of 5% solution of TritonX-100 in water containing 1% of pancreatin, USP Apparatus 2 (paddle) at 75 rpm. Tolerance: NLT* [redacted] (b) (4) *% (Q) of each EPA and DHA quantity as determined in Assay is dissolved in 60 minutes*

or alternatively

- [redacted] (b) (4)

Introduction

FDA's Division of Bioequivalence, DBE has requested Par to modify its previously proposed dissolution method for Omega-3 Acid Ethyl Esters Capsules, 1 g (refer to DBE's Bioequivalence deficiency letter, issued on February 17,2010). DBE recommended to further evaluate aqueous media containing Triton X-100 at (b) (4) concentrations, e.g. 5%, 8% and 10% using USP Apparatus 2 (paddle) at rotational speed (b) (4) 50, 75 and 100 rpm. It was also suggested evaluating USP Apparatus 3 and 4.

This report summarizes results of additional studies aimed to develop an acceptable dissolution method for Omega-3-acid Ethyl Esters Capsules, 1 gram, using Par's and RLD products.

(b) (4)

Experimental

Several media using Triton X-100 in water at different concentrations and at different rpm were evaluated. All experiments were carried out using Apparatus 2, paddle, and 900 mL of a medium. To prevent floating of the capsules, helix sinkers were used.

Note: Experiments where results obtained from the first six capsules demonstrated high variability at 60 minutes were discontinued. Results of such experiments are provided in this report in an abbreviated format, i.e. average, max and min values, and % RSD.

1, **Triton X-100, 5% in water,**

Table 1 summarizes results obtained with Triton **X-100, 5%** in DI water, Apparatus 2, paddle, at 50 rpm, 75 rpm and 100 rpm.

Table 1. Dissolution in 5% Triton X-100 in water, Apparatus 2, various RPM.

Product Name: Omega-3-acid Ethyl Esters Capsules, 1g, Batch/lot #699982/216809						
Dissolution Medium 5% Triton X-100 solution in water, Apparatus 2						
Date: 03/08/2010						
RPM	**Content**		**% Dissolved**			
			15 min	**30 min**	**45 min**	**60 min**
50	EPA	**Avg**	0.4	1.3	7.2	24.6
		RSD	245	155	153	114.1
		Max	(b) (4)			
		Min				
	DHA	**Avg**	0	1.5	7.8	25.9
		RSD	N/A	155	152	118
		Max	(b) (4)			
		Min				
75	EPA	**Avg**	0	0	6.9	24.1
		RSD	N/A	N/A	144	88
		Max	(b) (4)			
		Min				
	DHA	**Avg**	0	0	7.5	25.8
		RSD	N/A	N/A	142	92
		Max	(b) (4)			
		Min				
100	EPA	**Avg**	1.0	15.2	30.9	45.8
		RSD	245	129	86	80
		Max	(b) (4)			
		Min				
	DHA	**Avg**	1.1	16.7	33.3	48.8
		RSD	245	129	85	80
		Max	(b) (4)			
		Min				

2. **Triton X-100, 8% in water.**

Table 2 summarizes results obtained with Triton X-100, 8% in DI water, **Apparatus** 2, paddle, at 50 rpm, 75 rpm and 100 rpm.

Table 2. Dissolution in 8% Triton X-100 in water, Apparatus 2, various RPM.

Product Name: Omega-3-acid Ethyl Esters Capsules, 1g, Batch/lot #699982/216809						
Dissolution Medium 8% Triton X-100 solution in water, Apparatus 2						
Date: 03/09/2010						
RPM	**Content**		**% Dissolved**			
			15 min	**30 min**	**45 min**	**60 min**
50	EPA	**Avg**	**4.5**	**12.7**	**19.5**	**24.4**
		RSD	87	104	109	113
		Max	(b) (4)			
		Min				
	DHA	**Avg**	**4.3**	**13.0**	**20.4**	**25.8**
		RSD	93	105	110	114
		Max	(b) (4)			
		Min				
75	EPA	**Avg**	**0.8**	**3.0**	**10.3**	**18.7**
		RSD	172	149	137	140
		Max	(b) (4)			
		Min				
	DHA	**Avg**	**0.8**	**3.0**	**10.8**	**19.7**
		RSD	168	150	139	141
		Max	(b) (4)			
		Min				
100	EPA	**Avg**	**7.0**	**43.1**	**55.8**	**61.1**
		RSD	245	93	79	78
		Max	(b) (4)			
		Min				
	DHA	**Avg**	**7.4**	**46.5**	**60.2**	**65.9**
		RSD	245	94	79	78
		Max	(b) (4)			
		Min				

3. Triton X-100, 10% in water.

Table 3 summarizes results obtained with Triton X-100, 10% in DI water, Apparatus 2, paddle, at 50 rpm, 75 rpm and 100 rpm.

Table 3. Dissolution in 10% Triton X-100 in water, Apparatus 2, various RPM.

Product Name: Omega-3-acid Ethyl Esters Capsules, 1g, Batch/lot #699982/216809						
Dissolution Medium 10% Triton X-100 solution in water, Apparatus 2						
Date: 03/10/2010						
RPM	Content		% Dissolved			
			15 min	30 min	45 min	60 min
50	EPA	Avg	2.0	4.4	11.7	32.2
		RSD	121	111	110	71
		Max	(b) (4)			
		Min				
	DHA	Avg	1.7	4.2	11.5	33.6
		RSD	126	112	110	72
		Max	(b) (4)			
		Min				
75	EPA	Avg	51.7	40.6	42.3	43.1
		RSD	202	112	112	111
		Max	(b) (4)			
		Min				
	DHA	Avg	55.9	43.5	45.5	46.8
		RSD	203	112	112	111
		Max	(b) (4)			
		Min				
100	EPA	Avg	22.1	73.2	99.9	98.9
		RSD	137	47	6.7	3.8
		Max	(b) (4)			
		Min				
	DHA	Avg	22.6	78.1	107.3	106.5
		RSD	142	48	6.8	3.7
		Max	(b) (4)			
		Min				

The above data demonstrated that acceptable results were obtained only with 10% solution of Triton X-100 in DI water at **100 rpm.** However, very high concentration of the surfactant makes use of these parameters in routine QC analyses questionable.

The experiments were continued using 5% solution of Triton X-100 in DI water with 1% of pancreatin. Results are summarized in tables below.

Table 4. Dissolution in 5% Triton X-100 in water with 1% of pancreatin, Apparatus 2, 50 RPM.

Product Name: Omega-3-acid Ethyl Esters Capsules, 1g, Batch/lot #699982/216809							
Date: 03/29 – 03/30/10							
Dissolution Medium: 5 % Triton X-100 solution in water with 1% of pancreatin; Apparatus 2, 50 rpm							
Component	RPM	Capsule		% Dissolved			
		#	Weight, mg	15 min	30 min	45 min	60 min
EPA	50	1					(b) (4)
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1442.2	21.2	47.4	67.6	81.4
		%RSD	2.4	27.2	11.3	8.6	6.1
		Max					(b) (4)
		Min					
DHA	50	1					(b) (4)
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1442.2	21.8	49.1	70.5	86.1
		%RSD	2.4	30.0	12.1	9.5	6.7
		Max					(b) (4)
		Min					

Table 5. Dissolution in 5% Triton X-100 in water with 1% of pancreatin, Apparatus 2, 50 RPM.

Product Name: Lovaza Capsules, 1g, Lot # 803040W						
Date: 04/07/10						
Dissolution Medium: 5 % Triton X-100 solution in water with 1% of pancreatin; Apparatus 2, 50 rpm						
Component	RPM	Capsule		% Dissolved			
		#	Weight, mg	15 min	30 min	45 min	60 min
EPA	50	1		(b) (4)			
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1422.4	15.8	43.2	63.1	77.7
		%RSD	0.8	19.9	12.9	9.4	6.7
		Max		(b) (4)			
		Min					
DHA	50	1		(b) (4)			
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1422.4	15.5	46.3	68.2	84.4
		%RSD	0.8	23.6	12.2	9.7	7.2
		Max		(b) (4)			
		Min					

Figure 1. Dissolution **in 5%** Triton **X-100 in water with** 1% **pancreatin at 50 rpm**

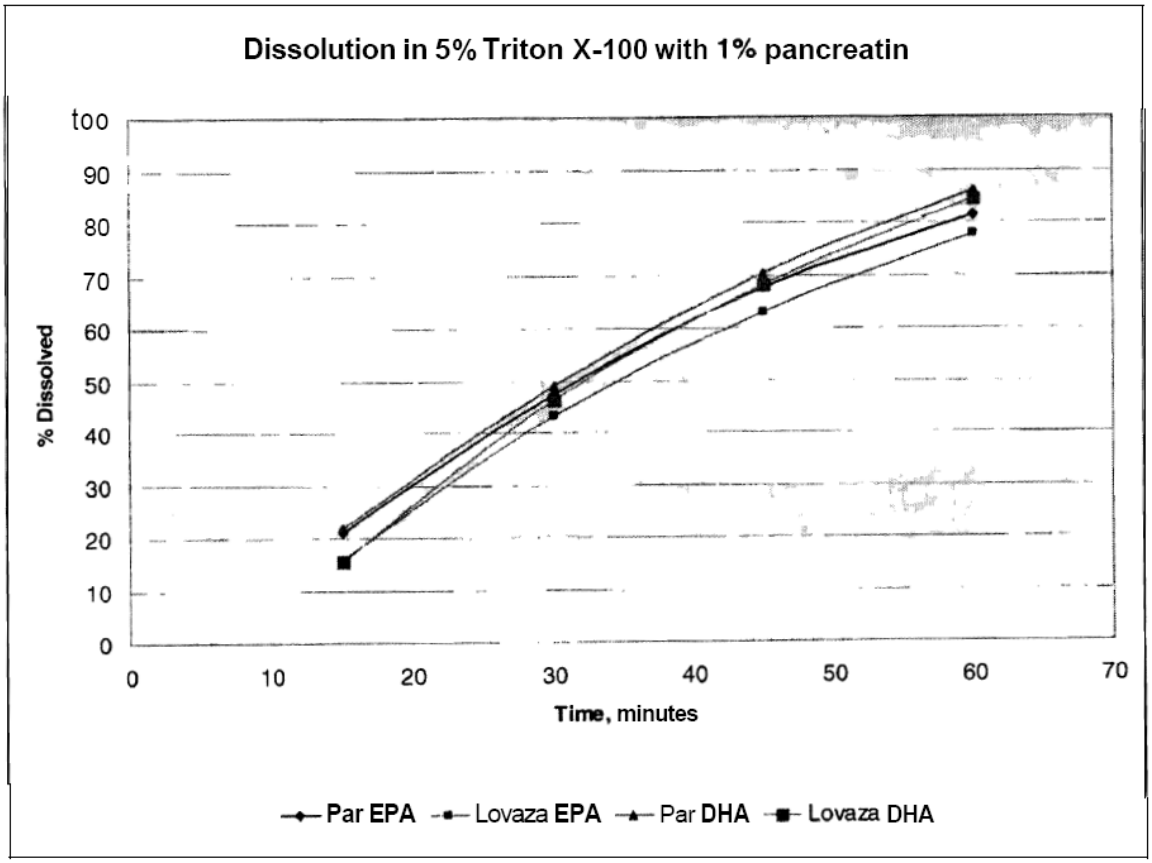

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Table 6. Dissolution in 5% Triton X-100 in water with 1% of pancreatin, Apparatus 2, 75 RPM.

Product Name: Omega-3-acid Ethyl Esters Capsules, 1g, **Batch/lot #699982/216809**							
Date: 03/26 – 03/329 10							
Dissolution Medium: 5 % Triton X-100 solution in water with 1% of pancreatin; **Apparatus 2, 75 rpm**							
Component	**RPM**	**Capsule**		**% Dissolved**			
		#	**Weight, mg**	**15 min**	**30 min**	**45 min**	**60 min**
EPA	75	1		(b) (4)			
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	**1441.1**	**50.4**	**76.4**	**89.4**	**95.1**
		%RSD	**3.6**	**36.7**	**16.8**	**8.9**	**5.3**
		Max		(b) (4)			
		Min					
DHA	75	1		(b) (4)			
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	**1441.1**	**53.6**	**81.4**	**96.0**	**102.6**
		%RSD	**3.6**	**36.6**	**16.9**	**8.9**	**4.9**
		Max		(b) (4)			
		Min					

Table 7. Dissolution in 5% Triton X-100 in water with 1% of pancreatin, Apparatus 2, 75 RPM.

Product Name: Lovaza Capsules, 1g, Lot # 803040W						
Date: 03/31/10						
Dissolution Medium: 5 % Triton X-100 solution in water with 1% of pancreatin; Apparatus 2, 75 rpm						
Component	RPM	Capsule		% Dissolved			
		#	Weight, mg	15 min	30 min	45 min	60 min
EPA	75	1	(b) (4)				
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1422.9	42.2	71.4	87.3	94.5
		%RSD	0.5	29.5	12.9	5.4	2.4
		Max	(b) (4)				
		Min					
DHA	75	1	(b) (4)				
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1422.9	45.2	77.0	94.4	102.8
		%RSD	0.5	30.6	13.2	5.9	2.8
		Max	(b) (4)				
		Min					

Figure **2. Dissolution in 5% Triton X- 100 in water with** 1% **pancreatin at 75 rpm**

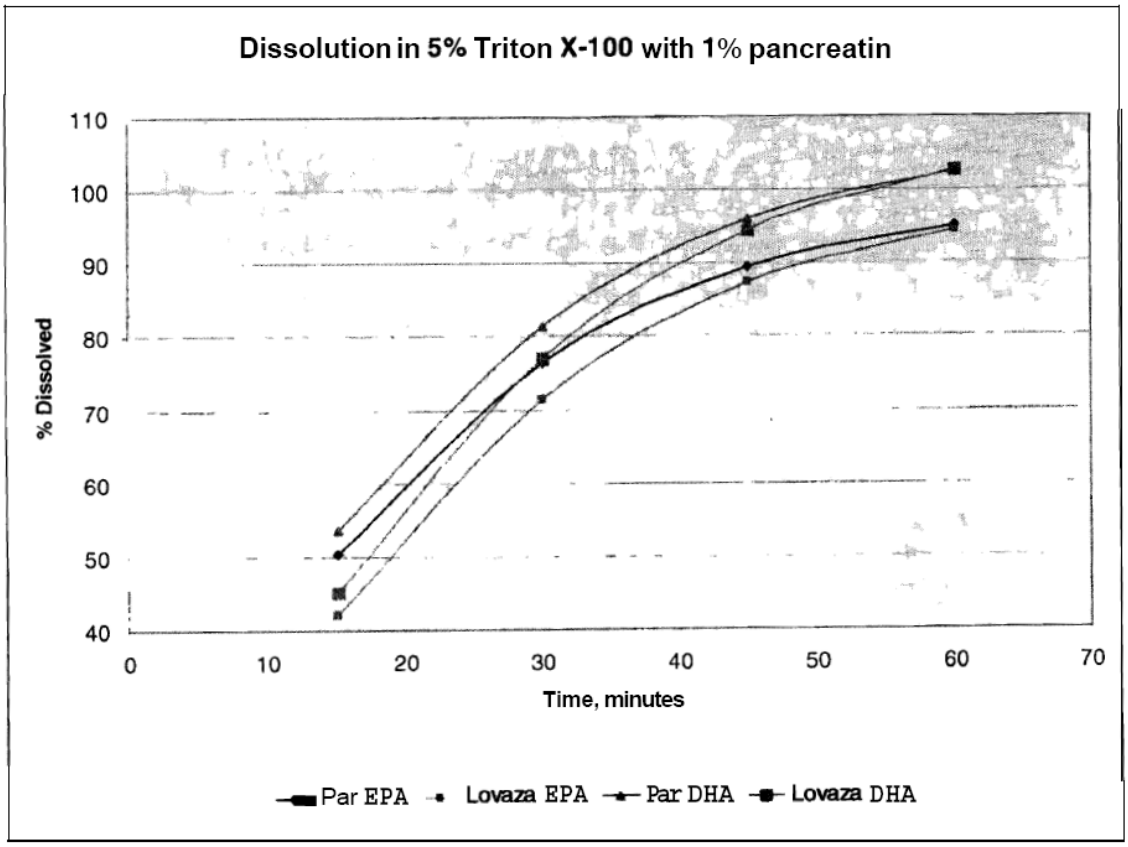


Table 8. Dissolution in 5% Triton X-100 in water with 1% of pancreatin, Apparatus 2,100 RPM.

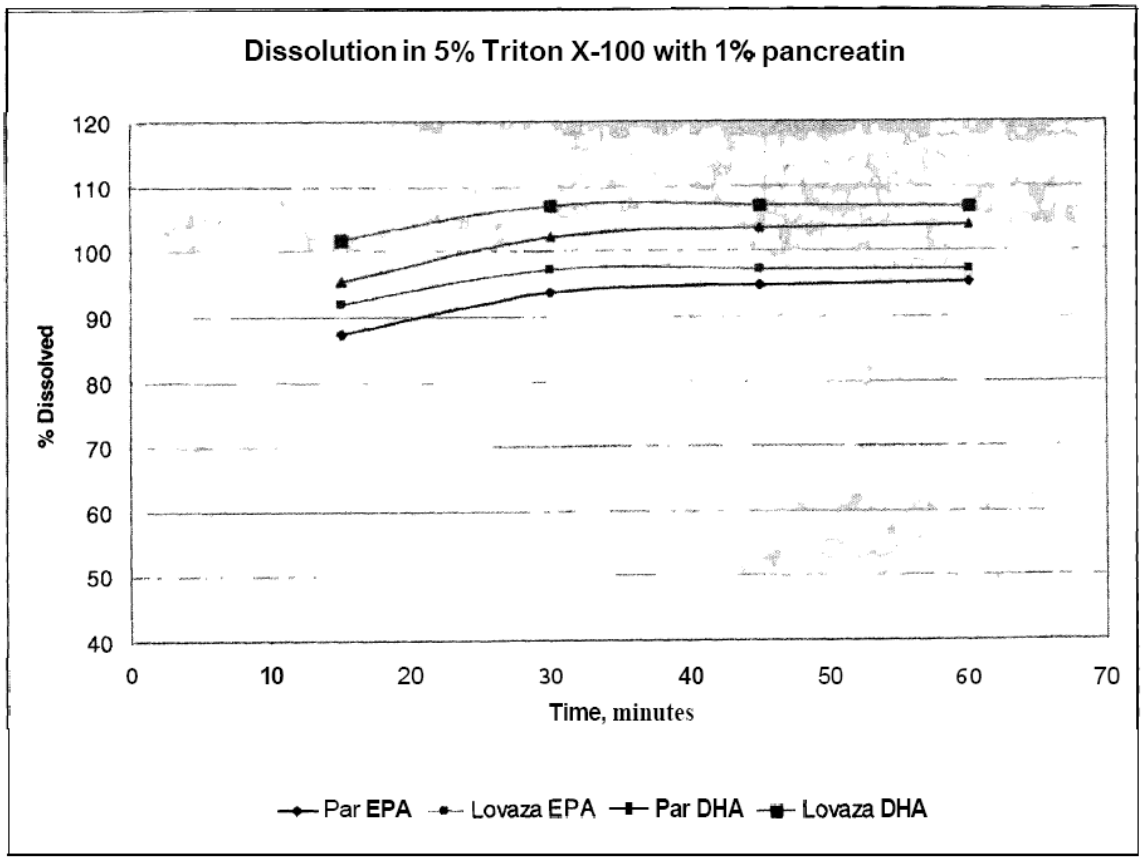
Product Name: Omega-3-acid Ethyl Esters Capsules, 1g, Batch/lot #699982/216809							
Date: 04/02/10							
Dissolution Medium: 5 % Triton X-100 solution in water with 1% of pancreatin; Apparatus 2,100 rpm							
Component	RPM	Capsule		% Dissolved			
		#	Weight, mg	15 min	30 min	45 min	60 min
EPA	100	1	(b) (4)				
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1415.9	87.3	93.6	94.9	95.3
		%RSD	2.7	15.2	7.0	4.3	3.6
		Max	(b) (4)				
		Min					
DHA	100	1	(b) (4)				
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1415.9	95.4	102.3	103.5	104.1
		%RSD	2.7	15.2	7.2	4.5	3.6
		Max	(b) (4)				
		Min					

Table 9. Dissolution in 5% Triton X-100 in water with 1% of pancreatin, Apparatus 2,100 RPM.

Product Name: Lovaza Capsules, 1g, Lot # 803040W							
Date: 04/08/10							
Dissolution Medium: 5 % Triton X-100 solution in water with 1% of pancreatin; Apparatus 2, 100 rpm							
Component	RPM	Capsule		% Dissolved			
		#	Weight, mg	15 min	30 min	45 min	60 min
EPA	100	1					
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1417.6	92.0	97.1	97.2	97.1
		%RSD	0.5	3.7	0.4	0.4	0.4
		Max					
		Min					
DHA	100	1					
		2					
		3					
		4					
		5					
		6					
		7					
		8					
		9					
		10					
		11					
		12					
		Avg	1417.6	101.7	107.1	107.1	106.8
		%RSD	0.5	3.8	0.5	0.4	0.5
		Max					
		Min					

(b) (4)

Figure *3*. Dissolution in *5%* **Triton X-100 in water with 1% pancreatin at 100 rpm**



The data demonstrate that addition of 1% pancreatin to 5% aqueous solution of Triton X-100 significantly improved capsule shells' solubility. Even at 50 rpm all capsules of Par and brand products have released some amount of oil, at least (b) (4)%. Evidently, the rate of dissolution as well as precision of the results was proportional to rotational speed.
Comparison of the dissolution rates between Par's generic product and the brand product showed a great degree of similarity. The f_2 similarity factors calculated using the following equation

$$f_2 = 50 \times \log \{[1 + \frac{1}{n} \sum_{t=1}^{n} (Rt - Tt)^2]^{-0.5} \times 100\}$$

are summarized below,

Table 10. Similarity factors

Dissolution in 5% Triton X-100 in water with 1% pancreatin at different rpm Omega-3-acid Ethyl Esters Capsules, 1 g vs Lovaza			
Component	50 rpm	75 rpm	100 rpm
EPA	66.8	64.9	73.3
DHA	70.7	65.4	66.6

All f_2 values were greater than 50.0, thus satisfying the similarity requirement.

Additional experiments
An attempt to employ USP Apparatus 3 was made. (b) (4)

Conclusion

Based on the presented data it can be concluded that dissolution of Omega-3-acid Ethyl Esters Capsules can be carries out using 5% solution of Triton X-100 in water containing 1% of pancreatin as medium. Par proposes two sets of specification as follows:

- 900 mL of 5% solution of Triton X-100 in water containing 1% of pancreatin, USP Apparatus 2 (paddle) at 75 rpm. Tolerance: Not less than (b) (4)% (Q) of each EPA and DHA quantity as determined in Assay is dissolved in 60 minutes,
  or alternatively
- (b) (4)

REVIEWER'S COMMENTS: The firm's responses to Deficiency #1 and 2 are **incomplete.**

- Omega-3-Acid Ethyl Esters are practically insoluble in water and very soluble in alcohols, e.g. methanol, ethanol, isopropanol, acetone, heptane and petroleum ether. Omega-3-Acid Ethyl Esters contains predominantly eicosapentaenoic (EPA) and docosahexaenoic acid (DHA).

- In its original application (submission date November 10, 2008), the firm only conducted a disintegration test per USP <711>. In its 1st dissolution amendment

(submission date September 30, 2009), the firm submitted the development of the quantitative rupture test report using water with different surfactants, i.e. (b) (4) [redacted] In additional, the firm also conducted the dissolution testing using Triton X-100 (b) (4) [redacted] (b) (4) Triton X-100) with and without pepsin, as the dissolution medium. Based on the dissolution data the firm submitted, only Trixon-100 appears to be the most promising surfactant among all others. DBE recommended the firm to repeat the comparative quantitative capsule rupture test with **various** (b) (4) Triton X-100 concentrations in water with USP Apparatus 2 (paddle) at various (b) (4) **agitation** speeds.

- In the current amendment, the firm has provided the additional dissolution data per DBE's requests. All the dissolution testing was used the USP Apparatus 2 (paddle). The firm claimed that the USP Apparatus 3 was also tested, (b) (4) (b) (4) The following summarizes the outcomes of the dissolution testing under various conditions the firm submitted in the current submission:

  1) Dissolution testing using <u>water as the dissolution medium with different concentrations of Triton X-100 (5%, 8% and 10%) with various agitation speeds (50 rpm, 75 rpm and 100 rpm):</u> The results showed the incomplete dissolution profiles (see Table 1 and 2) with 5% and 8% Triton X-100. The complete dissolution profile was obtained only with 10% Triton X-100 at 100 rpm. The firm stated that very high concentration of the surfactant makes use of these parameters in routine QC analyses questionable.

  2) Dissolution testing using <u>5% Triton X-100 in water with 1% pancreatin as the dissolution medium with various agitation speeds (50 rpm, 75 rpm and 100 rpm):</u> The results demonstrated that additional of 1% pancreatin to 5% Triton X-100 significantly improved test products solubility. The drug released rated and precision of the results was proportional to rotational speed. But at 100 rpm (see Table 8 and 9), the test products demonstrated very rapid dissolution at early time points (e.g., at 15 min, (b) (4) % was dissolved for EPA and (b) (4) % was dissolved for DHA).

- Combined the dissolution data from 1st dissolution amendment and current submission using water as the dissolution medium with Triton X-100, the firm conducted the following 7 sets of dissolution testing conditions using Apparatus 2 (paddle). The reviewer noticed that all the dissolution testing was done on **unexpired biolots.** The test biolot # 21680902 was 11 to 13 months old in the 1st amendment. The test biolot # 21680902 was 20 months old in the current amendment.

1. (b) (4)
2.
3.
4. 5% Triton X-100 at 50, 75 and 100 rpm
5. 8% Triton X-100 at 50, 75 and 100 rpms
6. 10% Triton X-100 at 50, 75 and 100 rpms
7. 5% Triton X-100 + 1% pancreatin at 50, 75 and 100 rpms

The reviewer rejected those dissolution conditions where (b) (4) (b) (4) only the 7 set was eligible for consideration. The % dissolution at 60 minutes of the 7th set is shown below.

DRUG	RPM	Mean % EPA	Range EPA	Mean % DHA	Range DHA
TEST	50	81.4	(b) (4)	86.1	(b) (4)
RLD	50	77.7		84.4	
TEST	**75**	95.1		102.6	
RLD	**75**	94.5		102.8	
TEST	100	95.3		104.1	
RLD	100	97.1		106.8	

Based on the dissolution data above the reviewer recommends the following method and specification which the test drug product will meet at the S1 level. Please see the tables below for the details.

Medium:	Water + 5% Triton X-100 with 1% pancreatin*
Apparatus:	USP apparatus 2 (paddle)
Speed:	75 rpm
Volume:	900 mL
Specification:	NLT (b) (4)% (Q) of EPA and DHA is dissolved in 60 minutes.

The 2 tier dissolution testing was not recommended (b) (4)

*1% pancreatin solution was prepared according to the USP Chapter <711> specification to have protease activity that did not exceed (b) (4) units.

EPA:

Dissolution Conditions	**Apparatus:**	II (Paddles)
	Speed of Rotation:	75 rpm
	Medium:	5% Triton X-100 solution in water with 1% pancreatin
	Volume:	900 mL
	Temperature:	37 +/- 0.5 °C
Firm's Proposed Specification	NLT (b) (4) % (Q) of EPA is dissolved in 60 minutes	
Dissolution Testing Site (Name, Address)	Par Pharmaceutical, Inc.	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15 min	30 min	45 min	60 min	Study Report Location
Study Report# MS10-013-0	3/26/2010 - 3/29/2010	Omega-3-acid Ethyl Esters Capsules (Lot #699982/216809) Mfr. Date: 07/17/08	1 g Capsules	12	Mean	50.4 %	76.4 %	89.4 %	95.1 %	p.9 and 10
					Range	(b) (4)				
					%CV	36.7	16.8	8.9	5.3	
Study Report# MS10-013-0	3/31/2010	Lovaza ® Capsules (Lot #803040W) Exp. Date: Apr 2011	1 g Capsules	12	Mean	42.2 %	71.4 %	87.3 %	94.5 %	
					Range	(b) (4)				
					%CV	29.5	12.9	5.4	2.4	

DHA:

Dissolution Conditions	**Apparatus:**	II (Paddles)
	Speed of Rotation:	75 rpm
	Medium:	5% Triton X-100 solution in water with 1% pancreatin
	Volume:	900 mL
	Temperature:	37 +/- 0.5 °C
Firm's Proposed Specification	NLT (b) (4) % (Q) of DHA is dissolved in 60 minutes	
Dissolution Testing Site (Name, Address)	Par Pharmaceutical, Inc.	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**				**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	
Study Report# MS10-013-0	3/26/2010 - 3/29/2010	Omega-3-acid Ethyl Esters Capsules (Lot #699982/216809) Mfr. Date: 07/17/08	1 g Capsules	12	Mean	53.6 %	81.4 %	96.0 %	102.6 %	p.9 and 10
					Range	(b) (4)				
					%CV	36.6	16.9	8.9	4.9	
Study Report# MS10-013-0	3/31/2010	Lovaza ® Capsules (Lot #803040W) Exp. Date: Apr 2011	1 g Capsules	12	Mean	45.2 %	77.0 %	94.4 %	102.8 %	
					Range	(b) (4)				
					%CV	30.6	13.2	5.9	2.8	

- The firm has proposed two dissolution methods with two specifications: 1) Method 1: 900 mL of 5% Triton X-100 in water with 1% pancreatin using USP Apparatus 2 (paddle) at 75 rpm. Specification: NLT (b)(4)% (Q) of each EPA and DHA is dissolved in 60 minutes; and 2) Method 2: (b) (4) (b) (4) (b) (4)

  The firm's proposed Method 1 is acceptable but the DBE proposes a specification (NLT (b)(4)% (Q) of EPA and DHA). The DBE requests the firm to accept and acknowledge the method and specification.

A. Comment

In the current amendment, the firm submitted additional dissolution data per DBE's requests. Based on the dissolution data the firm submitted, DBE recommends the following dissolution method and specification: 900 mL of 5% Triton X-100 in water with 1% pancreatin using USP Apparatus 2 (paddle) at 75 rpm. Specification: NLT (b)(4)% (Q) of each EPA and DHA is dissolved in 60 minutes. **The DBE requests the firm to confirm the Method and specification. The dissolution testing is incomplete.**

B. Deficiency Comment:

The firm should accept and acknowledge FDA-recommended dissolution method and specification.

C. Recommendation

The *in vitro* dissolution testing conducted by Par Pharmaceutical Inc. on its test product, (b) (4) Omega-3-acid ethyl esters Capsules, 1 g, comparing them to Smithkline Beecham's Lovaza® Capsules, 1 g, is **incomplete** pending the firm's acceptance of the DBE-recommended dissolution method and specification.

(b) (4)

[redacted]

D. Dissolution Consulting

From: Munshi, Utpal
Sent: Thursday, July 01, 2010 11:13 AM
To: Ren, Ke
Subject: RE: Requests for dissolution consult on Omega-3 Acid Ethyl Esters Capsules, ANDA 091018

Hi Ke:
The firm has submitted a number of different methods that generally follow the suggestions that you gave them in your February 3, 2010 review. The data presented in the dissolution development report in the current amendment clearly show that in the absence of pancreatin, the methods using 5% to 10% Triton X-100 with rotation speeds anywhere from 50 to 100 rpm yield unacceptable data (low dissolution and/or high variability). However, in the presence of 1% pancreatin, the method using 5% Triton X-100 is much more promising.

In the presence of 1% pancreatin, the firm has used three different speeds, 50 rpm, 75, rpm, and 100 rpm. 100 rpm is unacceptable given that it is not discriminatory. The 75 rpm method is a little better. However, there is fairly high variability (approx. (b) (4) % at 30 minutes) even at (b) (4)% dissolution. The pick of the three speeds for both EPA and DHA is 50 rpm. While there still high variability at 30 minutes (approximately (b) (4)%), dissolution is only (b) (4)%. Variability reduces to acceptable levels ((b) (4)%) when (b) (4)% dissolution is achieved. While there is high variability at 15 and 30 minutes, and maybe there are ways of reducing it, I think given the nature of the product, it might not be worth everyone's time to pursue this issue any further. That being said, there are a few issues that I think the firm should address before we accept the method and issue specifications. First, while the average dissolution is above (b) (4)% for both DHA and EPA for the Test product, not all units have reached the (b) (4)% threshold (i.e., what we consider to be complete dissolution). As a result, I would like the firm to extend the dissolution testing out to 75 minutes and 90 minutes (in other words, add sampling time points so

that we get all units being above (b)(4)%). Secondly, as noted above, the firm has used pancreatin. While we usually use an enzyme in the context of Tier I/II testing (see Dissolution <711>), there is a precedent for the DBE allowing the use of enzyme outside of this paradigm in the context of products similar to your product. (See DARRTS, ANDA 201687, my dissolution consult in Santhosh's review dated 5/7/2010). However, USP Chapter 711 states that the maximum protease activity of pancreatin should be 1750 USP units per 1000 mL. The firm should state the activity of 1% pancreatin in the context of 5% Triton X-100 in water. If the activity is above the stated threshold, the firm may have to add less pancreatin and generate new dissolution data accordingly.

Please let me know if you have any questions.

Please note that the above are just recommendations. Please consult your Team Leader for additional input and decision-making.

Thanks,
Utpal

From: Ren, Ke
Sent: Friday, June 25, 2010 10:36 AM
To: Munshi, Utpal
Subject: Requests for dissolution consult on Omega-3 Acid Ethyl Esters Capsules, ANDA 091018

Hello Utpal:

This is a 2nd dissolution amendment. It is an electric submission (submission date 5/5/2010).

Background: Omega-3-Acid Ethyl Esters are insoluble in water and very soluble in alcohols, e.g. methanol, ethanol, isopropanol, acetone, heptane and petroleum ether. DBE recommended the firm to develop a quantitative rupture test for the test product. Based on the firm's dissolution development report (1st dissolution amendment), the firm investigated the dissolution testing using (b)(4)% Triton X-100 in water gave the most promising surfactant among all others. DBE recommended the firm to repeat the quantitative capsule rupture test with **various** (b)(4) Triton X-100 concentrations in water medium (5% Triton X-100, 8% Triton X-100 and 10% Triton X-100) with USP Apparatus 2 (paddle) at various (b)(4) **agitation** speeds (50 rpm, 75 rpm and 100 rpm) or to explore other testing conditions.

In the current submission, the firm proposed the two dissolution methods: 1) 900 mL of 5% Triton X-100 in water contain 1% of pancreatin with USP Apparatus 2 at 75 rpm; 2) (b)(4) I think Method 2 gave none discretionary result. But the Method 1 showed high variability at 15 min and 30 min time points.

Any suggestions on the dissolution method and specifications?

Thanks,

Ke

BIOEQUIVALENCE DEFICIENCY

ANDA: 091018

APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

Your dissolution testing data comparing your product, Omega-3-Acid Ethyl Esters Capsules, 1 g, with the reference product SmithKline's Lovaza® Capsules, 1 g, using your proposed Method I are acceptable. However, your proposed specification for this proposed method I is not acceptable. Based on the data submitted, the DBE recommends more appropriate specification below.

Compared with your proposed Method I, your proposed Method II is not considered sufficiently discriminatory, and therefore, not acceptable.

Please acknowledge your acceptance of the following dissolution method and specification:

Medium	5% Triton X-100 in water with 1% pancreatin
Volume	900 mL
Temperature	37°C
USP Apparatus	II (paddles)
Rotational Speed	75 rpm
Specification	NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 60 minutes

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. Completed Assignment for ANDA 091018

Reviewer: Ren, Ke **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Omega-3-Acid Ethyl Esters Capsules, 1 g, Par Pharmaceutical Inc.

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
11717	5/5/2010	Other	Dissolution Amendment	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91018	ORIG-1	PAR PHARMACEUTICAL	OMEGA-3-ACID ETHYL ESTERS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KE REN
08/10/2010

SHRINIWAS G NERURKAR
08/10/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
08/11/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091018		
Drug Product Name	Omega-3 Acid Ethyl Esters Capsules		
Strength(s)	1 g		
Applicant Name	Par Pharmaceutical Inc.		
Address	One Ram Ridge Road Spring Valley, New York 10977		
Applicant's Point of Contact	Julie Szozda		
Contact's Telephone Number	845- 573- 5780		
Contact's Fax Number	845- 573- 5795		
Original Submission Date(s)	November 10, 2008		
Submission Date(s) of Amendment(s) Under Review	September 30, 2009		
Reviewer	Ke Ren. Ph.D.		
Study Number (s)	2008-1806	2008-1807	2008-1835
Study Type (s)	Fasting (single-dose study, RLD drug only)	Fed (single-dose study, RLD drug only)	Fed (single-dose, two-way crossover study)
Strength (s)	4 x 1 g	4 x 1 g	4 x 1 g
Clinical Site	Pharma Medica Research Inc.		
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6		
Analytical Site	(b) (4)		
Analytical Site Address			
Overall Review Result	**INADEQUATE**		
Bioequivalence Study Tracking/supporting Document#	**Study / Test Type**	**Strength**	**Review Result**
7	Dissolution	1 g	**INADEQUATE**

I. Executive Summary

This is a dissolution amendment review.

Par Pharmaceutical Inc.'s submitted its response to the deficiency comments made by the Division of Bioequivalence (DBE) in its letter dated May 6, 2009. The firm was asked to submit individual disintegration data for the test and reference products, and details of disintegration test information. In addition, the DBE recommended the firm to develop a quantitative rupture test for the test product and submit the long term storage stability data.

In the current amendment, the firm submitted individual disintegration data for the test and reference products, details of disintegration test information and long term storage stability data per DBE's requests.

For the development of the quantitative rupture test, the firm first investigated using water with different surfactants, i.e. (b) (4) Based on the dissolution data the firm submitted, these methods are associated with various drawbacks indicating that they are not appropriate quantitative rupture test method for this drug product (refer to Reviewer's Comments #2 for details).

Next, the firm also investigated the dissolution testing using (b) (4) The Trixon-100 appears to be the most promising surfactant among all others (refer to Reviewer's Comments #2 for details). However, the firm is recommended to modify the dissolution testing parameters to further improve this method.

The firm is recommended to conduct further investigation to find an appropriate *in vitro* testing method for this drug product. The DBE recommends the following:

1. The firm may repeat the comparative quantitative capsule rupture test with **various** (b) (4) Triton X-100 concentrations in water medium (5% Triton X-100, 8% Triton X-100 and 10% Triton X-100) with USP Apparatus 2 (paddle) at various (b) (4) **agitation** speeds (50 rpm, 75 rpm and 100 rpm).

Medium:	Water + (**5% Triton X-100, or 8% Triton X-100, or 10% Triton X-100**)
Apparatus:	USP apparatus II (paddle)
Speed:	**50 rpm, or 75 rpm, or 100 rpm**
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

If necessary, the firm may try varying the media volume, and/or using USP Apparatus IV (flow-through Cell) or USP Apparatus III (reciprocating cylinder) instead of Apparatus II (paddle) to avoid practical problems such as drug clogging on the basket's mesh. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

2. The firm is also encouraged to try other testing conditions in developing **quantitative capsule rupture** test for this drug product. The firm is referring to reference *USP PF Charter 35 (4) Stimuli to the Revision Process: Liquid-filled Gelatin Capsules* for its method development.

The DBE has requested a new site inspection from Division of Scientific Investigations (DSI) for the clinical site. The analytical site was last inspected in (b) (4) and outcome was (b) (4) (b) (4)

The DBE will review the bioequivalence studies at a later date.

Background

- The firm submitted its original application on November 10, 2008. The firm claimed that it conducted a disintegration test per USP <711>. However, the firm did not provide detail information for the disintegration test. DBE had done a "dissolution only" review on this ANDA (DARRTS ANDA 091018 Dissolution Review). The DBE asked the firm to submit the disintegration times of the individual capsules and detail information for the disintegration test.

- In addition, DBE recommended a **quantitative** rupture test method be used to evaluate the in vitro performance of the drug product. The firm was requested to develop own quantitative capsule rupture test. The firm was suggested to explore the following:

  Medium: 900 mL water with a low concentration of surfactant
  Apparatus: USP apparatus I (basket)
  Speed: 100 RPM
  Sampling: Once every 15 minutes until at least 80% of the labeled amount of drug is dispersed in the media

  If necessary, the firm was also suggested to try varying the medium volume, changing the rotational speed, adjusting the concentration of surfactant used, and/or using USP Apparatus II (paddles) instead of Apparatus I. It was informed that if all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

II. Table of Contents

III. Drug Product Information, PK/PD Information, and Relevant DBE History:

See the dissolution review of the original submission for the dissolution testing:
DARRTS ANDA 091018 (Dissolution Review)

IV. Review of Submission:

Following are the DBE's previous deficiency comments, the firm's current responses, and the reviewer's comments.

DEFICIENCY COMMENT #1*: Your disintegration testing is incomplete. Please submit the individual tablet data (disintegration times of the individual tablets) for the test and reference products. Additionally, a summary of the disintegration testing data should be provided in the eCTD table and should include the relevant information such as the apparatus, volume of the medium, testing dates, and batch numbers of the test and reference products used in testing.*

FIRM'S RESPONSE: *Disintegration test results of 12 individual tablets for the test and reference products are provided. The summary of the disintegration testing data is provided in the eCTD table format and includes the apparatus, volume of the medium, testing dates and batch numbers for the test and reference products used in testing.*

Summary of disintegration test for Omega-3-Acid Ethyl Esters Capsules, 1 gm vs. Lovaza Capsules in Water with Purified Pepsin.

Dissolution Conditions		Apparatus:	USP II (Paddle)			
		Speed of Rotation:	50 RPM			
		Medium:	Water (b) (4) (b) (4)			
		Volume:	500 mL			
		Temperature:	37.0°C ± 0.5°C			
Proposed Specifications		Meets requirements				
Dissolution Testing Site		Par Pharmaceutical, Inc.				
Reference	Product ID & Lot No.	Dosage Strength & Form	No. of Dosage Units	Capsule No.	Time, min	Study Report Location
05/28/09	Test Product: Omega-3-acid Ethyl Esters Capsules. Batch/Lot # 699982/216809 Mfr. Date: 07/17/08	1 gm, Capsules	12	1	(b) (4)	Par Pharmaceutical, Inc.
				2		
				3		
				4		
				5		
				6		
				7		
				8		
				9		
				10		
				11		
				12		
				Mean	1.3	
				%CV	66	
				High	(b) (4)	
				Low		
05/28/09	Test Product: Lovaza (Omega-3-acid Ethyl Esters) Capsules. Lot # 803040W Exp. APR 2011	1 gm, Capsules	12	1		
				2		
				3		
				4		
				5		
				6		
				7		
				8		
				9		
				10		
				11		
				12		
				Mean	4.2	
				%CV	33	
				High	(b) (4)	
				Low		

REVIEWER'S COMMENTS: The firm's response to Deficiency #1 is **complete.**

- The firm submitted 12 capsules individual disintegration data for the test and reference product. The disintegration test was conducted in 500 ml water (b) (4). The average of rupture time for the test and reference product is 1.3 min and 4.2 min, respectively. The firm's proposed specification of "all capsules rupture in not more than (b) (4) minutes".
- There is two-tier disintegration test in the OCPB review for NDA 021654. Tier 1 testing: The disintegration test is conducted in water in accordance with the current USP <701>. The specification for the disintegration release is NMT (b) (4) minutes. The specification for

the disintegration shelf-life is NMT 30 minutes[1]. If the capsules do not confirm to the acceptance criteria when tested in water, repeat the test in simulated gastric fluid. Tier 2 testing: The disintegration test is conducted in simulated gastric fluid (SGF)[2] as specified in USP <701>.

- The DBE asked the firm to submit individual unit disintegration testing data of the 12 dosage units of the test and reference products for completeness of the information on its disintegration testing report, and for possible future reference. Therefore, the firm's response to Deficiency #1 is **complete.**

DEFICIENCY COMMENT #2*: Currently, the DBE recommends a quantitative rupture test method be used to evaluate the in vitro performance of the drug product. Please develop your own quantitative capsule rupture method which should be discriminating to detect potential differences between the test and reference products. Please measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). You may consider trying the following method:*

Apparatus:	*USP apparatus I (basket)*
Speed:	*100 rpm*
Medium:	*Water with a low concentration of surfactant*
Volume:	*900 mL*
Sampling:	*Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA)and Docosahecaenoic acid(DHA)is dispersed in the media*

If necessary, we suggest you try varying the medium volume, changing the rotational speed, adjusting the concentration of surfactant used, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. Please provide individual capsule data as well as the test summary data such as mean, range, % coefficient of variation (CV) at each time point. The summary of the quantitative rupture testing data should also be provided in eCTD-formatted tables.

FIRM'S RESPONSE: *A significant body of data has been generated in an attempt to develop a meaningful quantitative rupture test method, one that would be sufficiently discriminating to detect potential difference between the test product, Omega-3-Acid Ethyl Esters Capsules, 1 gram, manufactured by Par and reference product, Levaza capsules 1 gram, manufactured by Catalent Pharma Solutions and marketed by Reliant Pharmaceuticals, Inc. Various rotation speeds, surfactant concentrations, and both USP Apparatus 1 and 2 were used as recommended by the Agency. Individual capsule data and the test summary data are provided.*

Omega-3-Acid Ethyl Esters Capsules, 1 g, Dissolution Method Development Report

[1] Note is made that the stability acceptance criteria is more relaxed at NMT (b) (4) minutes, (b) (4) (b) (4)

[2] Per the USP, Simulated Gastric Fluid is prepared by dissolving 2.0 g of sodium chloride and 3.2 g of ***purified pepsin***, which is derived from porcine stomach mucosa, with an activity of 800 to 2500 units per mg of protein, in 7.0 mL of hydrochloric acid and sufficient water to make 1000 mL.

Introduction

This report summarizes development efforts with regard to a dissolution method for Omega-3-acid Ethyl Esters Capsules, 1 gram manufactured by Par and Lovaza capsules 1 gram manufactured by Catalent Pharma Solutions and marketed by Reliant Pharmaceuticals, Inc.

Omega-3-acid Ethyl Esters, a lipid-regulating agent is supplied as liquid-filled soft gel capsules for oral administration. Each one gram capsule contains at least 900 mg of the ethyl esters of omega-3 fatty acids, predominantly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Omega-3-Acid Ethyl Esters are marine oil derived ethyl esters. Omega-3-Acid ethyl esters are obtained by the transesterification of the body oil of fat fish species coming from families such as *Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae and Scombridae* and subsequent physico-chemical purification processes. Omega-3 in the name refers to the third carbon-carbon bond from the carbon terminal end of the fatty acid molecule which is unsaturated. They are subject of a monograph in the current European Pharmacopoeia. However, current USP does not cover Omega-3-Acid Ethyl Esters capsules

Omega-3-Acid Ethyl Esters are practically insoluble in water and very soluble in alcohols, e.g. methanol, ethanol, isopropanol, acetone, heptane and petroleum ether.

Dissolution Method Development Background

Due to insolubility of Omega-3-Acid Ethyl Esters (Oil hereafter) in water, Par initially elected to include a rupture test as described in USP <2040>, e.g. for Dronabinol capsules, for finished product release and stability as a quality control tool.
In a Bioequivalency Amendment dated May 6, 2009, FDA requested Par to develop a quantitative capsule rupture test method capable to detect potential differences in in-vitro performance between Par's and reference, brand products. FDA suggested to start with the following method:

Medium:	Water with low concentration of a surfactant
Volume:	900 mL
Apparatus/Speed:	Apparatus 1, Basket at 100 rpm
Sampling:	Every 15 minutes until at least 80% of labeled amount of Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) is dispersed in the medium.

Number of units tested: 12

FDA also recommended to evaluate, if necessary different surfactants and dissolution apparatus 2.

Following this page, 12 Pages Withheld in Full as (b)(4)

Conclusion

As can be seen, a significant body of data has been generated in an attempt to develop a meaningful quantitative rupture test method, one that would be sufficiently discriminating to detect potential differences between the test and reference products. As suggested by FDA, various rotational speeds, surfactant concentrations, and both USP Apparatus 1 and 2 were used.

From the background and study data, we make the following observations.

Omega-3-acid ethyl esters are hydrophobic and insoluble in aqueous buffers. We investigated several media containing different surfactants, i.e. (b) (4)

(b) (4)

Therefore, based on the data and observations, and the noted difficulty in conducting the tests under the conditions recommended and used for this study, we question the relevance, purpose, and usefulness of a quantitative rupture test method for this particular product. Rather we conclude that the following supports the use of the USP Dissolution <711> rupture test as a quality control to confirm batch to batch consistency and release.

1. Product release includes a capsule rupture test, in accordance with USP <2040> **Disintegration and Dissolution of Dietary Supplements**. This test characterizes the capsule rupture rate, with the limit of not more than 15 minutes, and is being recommended for multiple USP products. These products include Calcifediol Capsules, Chloral Hydrate Capsules, Docusate Sodium Capsules, Dronabinol Capsules, etc.

   Par carried out a comparative study on the rupture test, results are presented in Table 8.
   As can be seen from the data, Par product meets USP requirements. Rupture rate of Par's product does not differ significantly from that of the RLD.

Table 8: Summary of Rupture Study for Omega-3-acid Ethyl Esters capsules, 1 gram vs. Lovaza capsules in water (b) (4)

Dissolution Conditions			
Apparatus: USP 2 (Paddle)			
Speed of Rotation: 50 RPM			
Medium: Water (b) (4)			
Volume: 500 mL			
Temperature: 37.0°C ± 0.5°C			
Number of Dosage Units: 12			
Date: 05/28/09			
Product ID & Lot No.	**Capsule No.**	**Capsule weight, mg**	**Time, min**
Omega-3-acid Ethyl Esters Capsules, 1 gram Batch/Lot # 699982/216809 Mfr. Date: 07/17/08	1	(b) (4)	
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
	Mean	**1416.7**	**1.3**
	%CV	**2.9**	**66**
	High	(b) (4)	
	Low		
Lovaza (Omega-3-acid Ethyl Esters) Capsules, 1 gram Lot # 803040W Exp. APR 2011	1		
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
	Mean	**1417.3**	**4.2**
	%CV	**0.3**	**33**
	High	(b) (4)	
	Low		

2. The capsule fill material of the Par product is very similar to that of the RLD within the variability of a naturally derived product. Omega-3-acid Ethyl Esters consist of several esterified fatty acids, mono- and polyunsaturated, as well as some saturated acids. The composition of API used in Par's product was evaluated along with fill material from three RLD lots. Results of seven ω-3 Omega-3-acid Ethyl Esters listed in the corresponding EP monograph are summarized in Table 9.

Table 9. Composition of Omega-3-acid Ethyl Esters API used in Par and Brand products (area percent)

Component	Brand lot #			Par's lot #
	127945	803040W	7HH0031	216809
Eicosahexaenoic acid EE (EPA)	52.6	53.0	53.5	53.5
Docosahexaenoic acid EE (DHA)	31.2	31.4	30.7	30.8
Octadecatrienoic acid EE (ALA)	0.1	0.1	0.1	0.1
Octadecatetraenoic EE (SPA)	3.4	3.4	3.5	3.1
Eicosatetraenoic acid EE (ETA)	0.8	0.7	0.7	0.3
Heneicosapentaenoic acid EE (HPA)	1.9	2.1	1.9	1.8
Docosapentaenoic acid EE (DPA)	3.4	2.7	2.8	2.1

3. There does not appear to be an in-vitro/in-vivo correlation in view of the generated dissolution data and the bioavailability study. The bioavailability study demonstrated that Par's Omega-3-acid Ethyl Esters Capsules, 1 gram, are bio-equivalent to Lovaza 1 gram Capsules. It also showed that for both products Tmax was about 6 hours.

REVIEWER"S COMMENTS FOR DEFICIENCY #2: The firm's response to Deficiency #2 is **incomplete.**

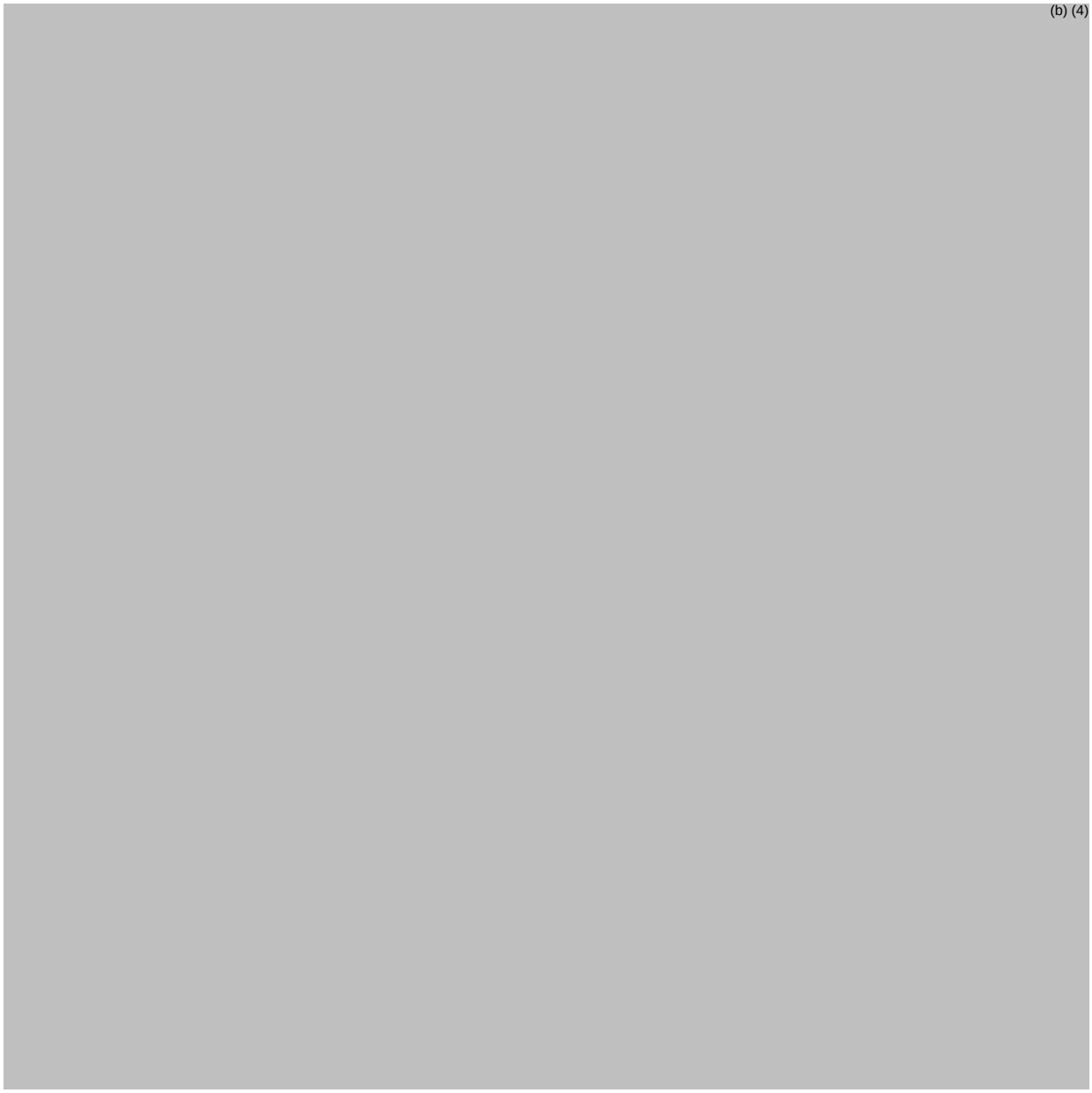
- Omega-3-Acid Ethyl Esters are practically insoluble in water and very soluble in alcohols, e.g. methanol, ethanol, isopropanol, acetone, heptane and petroleum ether. Omega-3-Acid Ethyl Esters contains predominantly eicosapentaenoic (EPA) and docosahexaenoic acid (DHA).

- The firm investigated water as the dissolution medium with various surfactants, i.e. (b) (4) [redacted]

- All dissolution testing were conducted by Apparatus II (paddles). (b) (4) [redacted]

- The following summarizes the outcomes of the dissolution testing under various conditions the firm submitted in its investigational report:

(b) (4) [redacted]



- Based on the dissolution data the firm submitted, it appears that the firm has not yet developed an appropriate quantitative rupture test method for this drug product. However, the Trixon-100 appears to be the most promising surfactant among all others.

- The firm questions the purpose and usefulness of a quantitative rupture test method for this drug. However, per USP PF Charter 35 (4) Stimuli to the Revision Process: Liquid-filled Gelatin Capsules[1], "*for capsules filled with a thick suspension or a waxy paste, a simple rupture of the shell may not adequately demonstrate that the finished dosage form is delivering the drug in a suitable manner. Measures of the dispersion and subsequent solubilization of the drug by the dissolution test also are required in order to evaluate the performance of the dosage*".

- This drug product is a soft gel formulation containing only oily ingredients (original submission date 11/10/2008, module 2). Please see the table below for the formulation. The DBE believes that a quantitative capsule rupture test characterizes the capsule shell rupture process as well as the dispersion of the active ingredient in the surrounding medium, and thus is a more appropriate way to describe the drug releasing process from its formulation. DBE management first recommended to its staff the need to use the quantitative capsule rupture test for soft gelatin capsules in which API is dissolved in an oily matrix at a staff meeting which took place on March 24, 2007 (DARRTS ANDA 040833 REV-BIOEQ-01 General Review).

Unit Composition for Omega-3-Acid Ethyl Esters Capsules					
Component	**Quality Standard**	**Function**	**Qty per Batch (kg)**	**mg/capsule**	**% composition**
(b) (4)					

- In the past, 0.5 N NaOH with 10% Triton X-100 as dissolution medium was found acceptable for ANDA091004 (Ergocalciferol Capsules, SigmaPharma, DARRTS 091004 General Review) for the quantitative capsule rupture test. The method is listed below:

  Medium: 900 mL of 0.5 N NaOH with 10% Triton X-100
  Apparatus: USP apparatus II (paddle)
  Speed: 100 RPM

  SigmaPharma claims that "*Oil can only be dissolved in non-polar solvents like hexane or toluene and saponified in basic solvents like NaOH. Therefore, a basic dissolution media*

has to be used in order to release the drug substance from oil based formulation. The release of Ergocalciferol from the oil based formulation can be facilitated by using a nonionic surfactant like Triton-X-100".

- However, the active ingredients in the current application are esters. (b) (4) (b) (4)

- The firm is recommended to further conduct further investigation to find an appropriate for this drug product: The DBE suggest that the firm explore the following:

  1. To achieve more gradual rupture and dispersion process, the firm should repeat the comparative quantitative capsule rupture test with **various** (b) (4) Triton X-100 concentrations in water medium (5% Triton X-100, 8% Triton X-100 and 10% Triton X-100) with USP Apparatus 2 (paddle), but at various (b) (4) **agitation** speeds (50 rpm, 75 rpm and 100 rpm). Based on the dissolution data submitted, it was suspected that the high paddle speed may have caused rupture of the capsules by sudden contact of the capsules with the paddle shaft, resulting in almost 100% dispersion following no (almost 0%) dispersion at the previous sampling times.

Medium:	Water + (**5% Triton X-100, or 8% Triton X-100, or 10% Triton X-100**)
Apparatus:	USP apparatus II (paddle)
Speed:	**50 rpm, or 75 rpm, or 100 rpm**
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

  If necessary, the firm may try varying the media volume, and/or using USP Apparatus IV (flow-through Cell) or USP Apparatus III (reciprocating cylinder) instead of Apparatus II (paddle) to avoid practical problems such as drug clogging on the basket's mesh. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

  2. The firm is also encouraged to try other testing conditions in developing **quantitative capsule rupture** test for this drug product. The firm is referred to the reference article, *USP PF Charter 35 (4) Stimuli to the Revision Process: Liquid-filled Gelatin Capsules* for helpful considerations in *vitro* release method development for the dosage form.

DEFICIENCY COMMENT #3: *Please provide long term storage stability data of free eicosapentaenoic acid and free docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid assay, which is at least 75 days. Please also provide long term storage stability data of eicosapentaenoic acid and docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid assay, which is at least 61 days.*

FIRM'S RESPONSE: *Long term storage stability data of free eicosapentaenoic acid and free docosahexaenoic acid in frozen plasma is included which covers the maximum storage time of the study samples for 75 days. In addition, long term storage stability data of eicosapentaenoic acid and docosahexaenoic acid in frozen plasma that covers the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acidassay for 61 days is also provided.*

REVIEWER'S COMMENTS: The firm's response to Deficiency #3 is **acceptable**. The firm has submitted the long-term stability data for *free eicosapentaenoic acid and free docosahexaenoic acid in frozen plasma* at $-70^0C \pm 10^0C$ and stored up to **80** days. The maximum storage period of biostudy samples for free eicosapentaenoic acid and free docosahexaenoic acid were **75** days. The storage duration was therefore within the established stability for free eicosapentaenoic acid and free docosahexaenoic acid in frozen plasma.

The firm has submitted the long-term stability data for *eicosapentaenoic acid and docosahexaenoic acid in frozen plasma* at $-70^0C \pm 10^0C$ and stored up to **63** days. The maximum storage period of biostudy samples for eicosapentaenoic acid and docosahexaenoic acid were **61** days. The storage duration was therefore within the established stability for eicosapentaenoic acid and docosahexaenoic acid in frozen plasma. The firm's response to Deficiency #3 is **acceptable.**

V. Deficiency Comments

Based on the dissolution data the firm submitted, it appears that the firm has not yet developed an appropriate quantitative rupture test method for this drug product. The firm is recommended to conduct additional testing (as listed in the recommendation section) with further modifications of its method with Triton-X-100, or using alternative USP apparatuses.

VI. Recommendations

The quantitative capsule rupture conducted by Par Pharmaceutical Inc. on its test products, Omega-3-acid ethyl esters Capsules, 1 g, comparing them to Smithkline Beecham's Lovaza® Capsules, 1 g, is **incomplete**.

The firm is recommended to further conduct further investigation to find an appropriate quantitative rupture test for this drug product. The DBE recommends the following:

1. The firm may repeat the comparative quantitative capsule rupture test with **various** (b) (4) Triton X-100 concentrations in water medium (5% Triton X-100, 8% Triton X-100 and 10% Triton X-100) with USP Apparatus 2 (paddle) at various (b) (4) **agitation** speeds (50 rpm, 75 rpm and 100 rpm).

Medium: Water + (**5% Triton X-100, or 8% Triton X-100, or 10% Triton X-100**)
Apparatus: USP apparatus II (paddle)
Speed: **50 rpm, or 75 rpm, or 100 rpm**
Volume: 900 mL

Sampling: Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

If necessary, the firm may try varying the media volume, and/or using USP Apparatus IV (flow-through Cell) or USP Apparatus III (reciprocating cylinder) instead of Apparatus II (paddle) to avoid practical problems such as drug clogging on the basket's mesh. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

2. The firm is also encouraged to try other testing conditions in developing **quantitative capsule rupture** test for this drug product. The firm is referred to the reference article, *USP PF Charter 35 (4) Stimuli to the Revision Process: Liquid-filled Gelatin Capsules* for its method development.

VII. Dissolution Consulting

From: Tampal, Nilufer
Sent: Tuesday, December 08, 2009 9:50 AM
To: Ren, Ke
Subject: FW: Requests for dissolution consult on Omega-3-Acid Ethyl Esters Capsules (rupture) 1 g, ANDA 091018

Hi Ke,

The firm is questioning the relevance, purpose and usefulness of the quantitative rupture test for its test product. The DBE ask for this test to use it as a QC tool for drug release (there are several examples including dronabinol, calcitriol, ergocalciferol where the NDA requires rupture test alone whereas the DBE asked the firms to develop a quantitative rupture test). Therefore, the firm may have to conduct additional testing. The firm attributed the variability in data with Apparatus 2 to the fact that the undissolved oil globules dispersed in the vessel were being aspirated during sampling. The firm may be able to address this issue by trying dissolution testing using apparatus 4. Also, the firm only tried water as the medium with different amounts of surfactants. For ergocalciferol, we found that 0.5N NaOH with 10% Triton X-100 as the dissolution medium works. In brief, the firm should try media other than water with different amounts of surfactants using apparatus 2, or try dissolution testing using apparatus 4.

Please consult your TL as well.

Thanks

Nilufer

From: Ren, Ke
Sent: Thursday, November 19, 2009 10:28 PM
To: Tampal, Nilufer
Subject: Requests for dissolution consult on Omega-3-Acid Ethyl Esters Capsules (rupture) 1 g, ANDA 091018

Hello Nilufer:

The file located in the EDR (ANDA 091018, letter date September 30, 2009). The firm was requested to develop own quantitative capsule rupture test method to evaluate the in vitro performance of the drug product. The firm investigated several media containing different surfactants, (b) (4) The USP **1092 General comments for the medium** states that "*Using an aqueous-organic solvent mixture as a dissolution medium is discouraged; however, with proper justification this type of medium may be acceptable*". I am not recommending to add (b) (4) in the medium unless the firm provide justification.

The firm found that Omega-3-Acid Ethyl Esters [redacted] (b) (4) However, there is huge variability due to the different capsule rupture time.

In the summary, the firm stated that " based on the data and observations, and the noted difficulty in conducting the tests under the conditions recommended and used for this study, the firm question the relevance, purpose and usefulness of a quantitative rupture test method for this particular product."

Any suggestion for the quantitative capsule rupture test?

In addition, there is no quantitative capsule rupture test in the NDA review. NDA only did the rupture test.
This ANDA is the first generic drug.

Thanks,

Ke

BIOEQUIVALENCE DEFICIENCIES

ANDA: 091018

APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence (DBE) has completed its review of the disintegration and quantitative rupture testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiencies have been identified:

As requested, you have explored different *in vitro* testing conditions in developing a quantitative rupture test method for the test product. Your method development report demonstrated that testing in (b) (4) media with the surfactants of (b) (4) were not suitable (b) (4) . On the other hand, the results of your testing in the aqueous media with different concentrations of the surfactant Triton X-100 have shown to be more promising. However, the paddle speed of (b) (4) rpm for this latter method was (b) (4). In addition, the testing results showed that the capsules were either intact (with almost 0% dispersed) or completely ruptured (with almost 100% dispersed) during the testing. It appeared that the (b) (4) paddle speed may have caused rupture of the capsules by sudden contact of the capsules with the paddle shaft, resulting in almost 100% dispersion following no (almost 0%) dispersion at the previous sampling times.

1. Therefore, the DBE recommends that you further modify the testing method with the aqueous media of Triton X-100 to achieve more gradual rupture and dispersion process, using (b) (4) concentrations of Triton X-100 concentrations and/or (b) (4) **agitation** speeds, as suggested below:

Medium:	Water + (**5% Triton X-100, or 8% Triton X-100, or 10% Triton X-100**)
Apparatus:	USP apparatus II (paddle)
Speed:	**50 rpm, or 75 rpm, or 100 rpm**
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid

(EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

If necessary, you may try varying the media volume.

2. Alternatively, you may consider using USP Apparatus IV (flow-through Cell) or USP Apparatus III (reciprocating cylinder) instead of Apparatus II (paddle) to avoid practical problems such as the oil floating to the surface of the medium and concentrating around the shaft. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. Please refer to the reference article, *USP PF Charter 35 (4) Stimuli to the Revision Process: Liquid-filled Gelatin Capsules* for helpful considerations in developing an *in vitro* testing method for similar dosage forms. As advised in this article, a quantitative capsule rupture test characterizes the capsule shell rupture process as well as the dispersion of the active ingredient in the surrounding medium, and thus is a more appropriate way to describe the drug releasing process from its formulation. The DBE currently recommend quantitative capsule rupture test be performed for all soft gel capsule products in which the Active Pharmaceutical Ingredient (API) is dissolved in an oily matrix.

   For the requested quantitative capsule rupture testing above, please use 12 units each of your Omega-3-Acid Ethyl Esters Capsules, 1 g, and the reference listed drug product, Lovaza®, 1 g, and provide the data for individual units as well as mean data, with CV% and range, for each test.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VIII. Outcome Page

Completed Assignment for ANDA 091018

Reviewer: Ren, Ke **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Omega-3-Acid Ethyl Esters Capsules, 1 g, Par Pharmaceutical Inc.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
10080	9/30/2009	Other	Dissolution Amendment	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91018	ORIG-1	PAR PHARMACEUTICAL	OMEGA-3-ACID ETHYL ESTERS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KE REN
02/03/2010

BING V LI
02/03/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/04/2010

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	91-018		
Drug Product Name	Omega-3-Acid Ethyl Esters Capsules		
Strength (s)	1 g		
Applicant Name	Par Pharmaceutical Inc.		
Address	One Ram Ridge Road Spring Valley, New York 10977		
Applicant's Point of Contact	Karen Rocco		
Contact's Phone Number	845- 639- 5152		
Contact's Fax Number	845- 639- 5201		
Submission Date(s)	November 10, 2008		
First Generic	Yes		
Reviewer	Ke Ren, Ph.D.		
Study Number (s)	2008-1806	2008-1807	2008-1835
Study Type (s)	Fasting (single-dose study, RLD drug only)	Fed (single-dose study, RLD drug only)	Fed (single-dose, two-way crossover study)
Strength(s)	4 x 1 g	4 x 1 g	4 x 1 g
Clinical Site	Pharma Medica Research Inc.		
Clinical Site Address	4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6		
Analytical Site	(b) (4)		
Analytical Site Address			
OUTCOME DECISION	**INCOMPLETE**		

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product, but the DBE recommends a quantitative capsule rupture test method for such dosage form. However, there is no specific DBE-recommended quantitative capsule rupture test method currently available in the public or internal dissolution database on the Office of Generic Drugs website (http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm).

The firm claimed that it conducted a disintegration test per USP <711>. However, the firm the results of the disintegration test. Details regarding the apparatus, medium, volume of the medium, testing dates were also not provided. The disintegration testing is **incomplete**. The firm should submit the individual disintegration data for the test and reference products.

In addition, DBE recommends the firm to develop a **quantitative capsule rupture** test to evaluate the in-vitro performance of Omega-3-acid Ethyl Esters Capsules. The quantitative capsule rupture method should be discriminating to detect potential differences between the test and reference products. The firm should measure drug release of two key components of the drug product, Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) as percentage of the labeled amounts. The firm may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

If necessary, the firm can try varying the media volume, increasing the rotational speed, increasing the concentration of surfactant, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

The Long Term Storage Stability (LTSS) for free eicosapentaenoic acid, free docosahexaenoic acid, eicosapentaenoic acid and docosahexaenoic acid are **under process**. The firm should submit LTSS for free eicosapentaenoic acid and free docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid, which is at least 75 days. The firm should also submit LTSS for eicosapentaenoic acid and docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid, which is at least 61 days.

The DBE requested Division of Scientific Investigations (DSI) inspection for clinical sit (new site). The analytical site was last inspected in (b) (4) and outcome was (b) (4) (b) (4)

The DBE will review the fasting and fed BE studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☐	☒	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☐	☒	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☐	☐	☒
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples*?			☐	☒	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

* The Long Term Storage Stability (LTSS) for free eicosapentaenoic acid, free docosahexaenoic acid, eicosapentaenoic acid and docosahexaenoic acid are **under process.**

Reviewer's Notes:

1. There is no USP method for Omega-3-acid ethyl esters capsules, but the DBE-recommends a quantitative capsule rupture test method for such dosage form. However, there is no specific DBE-recommended quantitative capsule rupture test method currently available in the public dissolution database on the Office of Generic Drugs (OGD) websites: http://www. fda.gov/cder/ogd.index.htm, nor in the DBE internal dissolution database.

2. The DBE recommends that the firm should develop their own quantitative capsule rupture method[1]. This method should be discriminating to detect potential differences between the test and reference products. The firm should measure drug release of two key components of the drug product, Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) as percentage of the labeled amounts. The firm may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

   If necessary, the firm can try varying the media volume, increasing the rotational speed, increasing the concentration of surfactant, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

3. As background information, the reviewer also checked the OCPB review of NDA 21-654 which listed a disintegration method[2] and specifications[3] for Omega-3-Acid Ethyl Esters capsules as follows:

   Two-tier disintegration test:

   Tier 1 Testing: The disintegration test is conducted in water in accordance with the current USP <701>.

   Specification: Disintegration release NMT (b) (4) min
   Disintegration shelf life* NMT 30 min

[1] V:\FirmsNZ\(b) (4)\Protocols\07012P0707.doc
[2] Chemistry review DFS N 021654 SCS 008 11-Apr-2006, page 3
[3] Chemistry review DFS N 021654 SCM 007 07-Feb-2006, page 13

* Note is made that the stability acceptance criteria is more relaxed at NMT (b) (4) minutes (b) (4)

If the capsules do not confirm to the acceptance criteria when tested in water, repeat the test in simulated gastric fluid.

Tier 2 Testing: The disintegration test is conducted in simulated gastric fluid (SGF)* as specified in USP <701>.

(b) (4)

However, per the USP, Simulated Gastric Fluid is prepared by dissolving 2.0 g of sodium chloride and 3.2 g of ***purified pepsin***, which is derived from porcine stomach mucosa, with an activity of 800 to 2500 units per mg of protein, in 7.0 mL of hydrochloric acid and sufficient water to make 1000 mL. (b) (4)

4. Currently, there is no control document review or Bioequivalence Recommendation Guidance for Omega-3-acid ethyl esters capsules. OGD Science Staff has **drafted** the bioequivalence recommendations for this product (see attachment for details). It recommends the disintegration testing be conducted according to the current USP <701>. Data should be provided for 12 capsules each of test and reference products. The acceptance limit for release is (b) (4) min and the limit for shelf-life is 30 min.

II. COMMENTS:

1. The firm did not provide the disintegration data for individual unit of the test and reference products. Details regarding the apparatus, medium, volume of the medium, testing dates were also not provided. Although this disintegration testing is not the current DBE-recommended method, the DBE is asking the firm to submit individual unit disintegration testing data of the 12 dosage units of the test and reference products for completeness of the information on its disintegration testing report, and for possible future reference. Additionally, a summary of the disintegration testing data should be provided in the eCTD table and should include the relevant information such as the apparatus (i.e. with or without the disc), volume of the medium, testing dates, and batch numbers of the test and reference products used in testing.

2. DBE recommends the firm to develop a **quantitative capsule rupture** test to evaluate the in-vitro performance of Omega-3-Acid Ethyl Esters Capsules. The quantitative capsule rupture method should be discriminating to detect potential differences between the test and reference products. The firm should measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). The firm may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

   If necessary, the firm can try varying the media volume, increasing the rotational speed, increasing the concentration of surfactant, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

3. The firm did not submit the LTSS for free eicosapentaenoic acid, free docosahexaenoic acid, eicosapentaenoic acid and docosahexaenoic acid.

4. The DSI inspection of the clinical facility has been requested.

III. DEFICIENCY COMMENTS:

1. The firm should submit the individual unit disintegration testing data of the 12 dosage units of the test and reference products conducted using the firm's disintegrating test method. Additionally, a summary of the disintegration testing data should be provided in the eCTD table and should include the relevant

information such as the apparatus (i.e. with or without the disc), volume of the medium, testing dates, and batch numbers of the test and reference products used in testing.

2. The firm should develop a **quantitative capsule rupture** test to evaluate the in-vitro performance of Omega-3-Acid Ethyl Esters Capsules.

3. The firm should submit LTSS for free eicosapentaenoic acid and free docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid (75 days). The firm should also submit LTSS for eicosapentaenoic acid and docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid (61 days).

4. The DSI inspection of the clinical facility has been requested.

IV. RECOMMENDATIONS:

The disintegration testing conducted by Par Pharmaceutical Inc. on its test products, Omega-3-acid ethyl esters Capsules, 1 g, comparing them to Smithkline Beecham's Lovaza® Capsules, 1 g, is **incomplete** due to the deficiencies cited in the deficiency comments section**.**

The firm should develop a **quantitative capsule rupture** test to evaluate the in-vitro performance of Omega-3-acid Ethyl Esters Capsules. The firm should measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). The firm may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

If necessary, the firm can try varying the media volume, increasing the rotational speed, increasing the concentration of surfactant, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile.

The firm should also submit individual disintegration testing data for the twelve (12) dosage units of test and reference products tested using the firm's disintegrating test method. Comparative disintegration profiles should include individual capsule data as well as the mean, range, and standard deviation for twelve capsules. Additionally, a summary of the disintegration testing data should be provided in the eCTD table and

should include the relevant information such as the apparatus (i.e. with or without the disc), volume of the medium, testing dates, and batch numbers of the test and reference products used in testing.

The firm should submit LTSS for free eicosapentaenoic acid and free docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid (75 days). The firm should also submit LTSS for eicosapentaenoic acid and docosahexaenoic acid that are sufficient to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid (61 days).

(b) (4)

Dissolution Test Method and Sampling Times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

(b) (4)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 91-018

APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence (DBE) has completed its review of the disintegration testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiencies have been identified:

1. Your disintegration testing is incomplete. Please submit the individual tablet data (disintegration times of the individual tablets) for the test and reference products. Additionally, a summary of the disintegration testing data should be provided in the eCTD table and should include the relevant information such as the apparatus, volume of the medium, testing dates, and batch numbers of the test and reference products used in testing.

2. Currently, the DBE recommends a quantitative rupture test method be used to evaluate the *in vitro* performance of the drug product. Please develop your own quantitative capsule rupture method which should be discriminating to detect potential differences between the test and reference products. Please measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). You may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA)and Docosahecaenoic acid(DHA)is dispersed in the media

Number of Units Tested: 12

If necessary, we suggest you try varying the medium volume, changing the rotational speed, adjusting the concentration of surfactant used, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. Please provide individual capsule data as well as the test summary data such as mean, range, % coefficient of variation (CV) at each time point. The summary of the quantitative rupture testing data should also be provided in eCTD-formatted tables.

3. Please provide long term storage stability data of free eicosapentaenoic acid and free docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid assay, which is at least 75 days. Please also provide long term storage stability data of eicosapentaenoic acid and docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid assay, which is at least 61 days.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA: 91-018

Reviewer: Ren, Ke **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Omega-3-acid Ethyl Esters Capsules, 1 g, Par Pharmaceutical Inc.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8044	11/10/2008	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ke Ren
5/1/2009 05:46:09 PM
BIOPHARMACEUTICS

Bing Li
5/1/2009 05:59:18 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
5/4/2009 11:59:53 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91018

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 34	PM: Chinyelum Olele

Electronic ANDA: Yes ☒ No ☐

ANDA #:091018
Firm Name: Par Pharmaceuticals Inc.
ANDA Name:Omega-3-Acid Ethyl Esters Capsules USP, 1 gram
RLD Name:Lovaza

Electronic AP Routing Summary Located:
V:\Chemistry Division III\Team 34\Electronic AP Summary\091018_APRV_ROUT_SUMRY

AP/TA Letter Located:
V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\091018_apltr

Project Manager Evaluation: **Date: 6/20/14 Initials:** KRD

for CO

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 11/10/08	Date of Application 11/10/08	Date Acceptable for Filing 11/10/08
Patent Certification (type) P-IV	Date Patent/Excl. expires 4/10/17	Citizens' Petition/Legal Case? Yes☒ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☒ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☐ Pending ☐☐ ☒ Acceptable ☐ OAI *EES Date Acceptable: 09/29/14* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 6/19/14 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 3/7/14 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 6/6/14 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

Methods Val. Samples Pending: Yes ☐ No ☐**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 6/5/14 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☒ Division

☒ Bob West / Peter Rickman

☒ Kathleen Uhl

☐Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 6/3/2014**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Lovaza Capsules NDA# 21-654 Date Checked 6/23/14 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day Maybe Is a forfeiture memo needed: Yes ☐ No ☒ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☒ No ☐☐	

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:

Comments:ANDA submitted on 11/10/2008, BOS=Lovaza NDA 21-654, PIV to '077, '667, '594, NCE exp 11/10/2009. Patent amendment rec'd on 1/12/2009-PIII to '594 exp. 8/4/2009. ANDA ack for filing with a PIV on 11/10/2008-this is the NCE minus one date (LO dated 3/9/2009).
Patent Amendment rec'd on 5/1/2009-notice sent via USPS to Pronova BioPharma Norge in Baerum, Norway and to GSK in both Philadelphia PA and Brentford GB with notices delivered on 3/20/2009(GB), 3/19/2009(US) and 3/23/2009(Norway), suit filed in D of DE on 4/29/2009 for infringement of the '077 and '667 patents, since this suit was filed within 45 days of notice for a drug product submitted on the NCE minus one date there was a 7.5 year stay of approval that expired on 5/10/2012.
Patent Amendment rec'd on 8/5/2010-PIV to the '488
Patent Amendment rec'd on 3/24/2011-for the '488: RR from GSK in Phila PA signed and dated 8/9/2010, RR from Pronova BioPharma in Baerum Norway signed but not dated, Par states that the original CA was amended to infringement of the '488 patent. As this patent was not present in the OB at the time this ANDA was submitted there can be no stay of approval related to this CA.
Patent Amendment rec'd on 5/21/2012-Letter from Latham and Watkins (counsel for Par) dated 5/18/2012: request for mtg with the Agency to discuss approval of this ANDA as well as request that the Agency confirm that 180 day exclusivity has not been forfeited.

Sponsor needs to submit a status update regarding the D of DE CA which at this point can only be related to the '667 patent as this is currently the only listed patent for Lovaza. Sponsor contacted via e-mail at 8:50 pm on Tuesday the 3rd of June and asked for status update.
If the CA was settled in Par's favor-which is likely considering this is the case for TEVA's ANDA which was already approved-then the Agency will be able to Fully Approve this ANDA. The same 180 day punt language that was used in TEVA's AP letter should also be incorporated into Par's AP letter.

Update 6/5/2014-Par submitted a patent amendment on 6/4/2014 indicating that Par obtained an appellate Court determination of invalidity of the asserted claims of the '667 patent with final judgment of invalidity of the asserted claims entered on 3/5/2014. Then on 6/5/2014 the sponsor submitted a patent amendment showing that CA 09 CV 0286 in the D of DE was dismissed with prejudice in relation to the '667 patent on 3/5/2014, this decision was in response to the ruling by the CAFC on 9/12/2013 which reversed the earlier finding of the D of DE and remanded back to the D of DE with orders to enter judgment in favor of appellants (TEVA and Par in this case).

ANDA is eligible for Final Approval.

2. ***Labeling Endorsement***

Reviewer, Betty Turner:
Date6/6/14

Labeling Team Leader, Theresa Liu for Ruby Wu:
Date6/6/14

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:
From: Liu, Theresa
Sent: Friday, June 06, 2014 9:56 AM
To: Turner, Betty; Olele, Chinyelum
Cc: Wu, Ruby (Chi-Ann)
Subject: RE: ANDA 91018

I concur. Thank you.

Theresa

From: Turner, Betty
Sent: Friday, June 06, 2014 8:03 AM
To: Olele, Chinyelum; Liu, Theresa
Cc: Wu, Ruby (Chi-Ann)
Subject: FW: ANDA 91018

Good morning Chi-Chi,

I have checked the USP, OB, MedWatch, Drugs@fda and DARRTS for changes. There are no pending supplements for the RLD in DARRTS. No changes for the labeling since the last review was completed.

AP Letter: In the address line, add a comma after Pharmaceuticals.

Thanks,

Betty

From: Olele, Chinyelum
Sent: Thursday, June 05, 2014 5:02 PMThe
To: Turner, Betty; Liu, Theresa
Cc: Wu, Ruby (Chi-Ann)
Subject: ANDA 91018

Hello,

This ANDA is ready for AP. Please provide labeling endorsement. Thanks

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read
OGD Regulatory Counsel

Date 23Jun2014
InitialsDTR

Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:AP letter okay. "Punt" language inlcuded.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 6/23/14**
Chemistry Div. **III (Sayeed)** **Initials rlw/for**

Comments: Chemistry Review #4 - Addendum #1 concluding that the CMC section of this ANDA is acceptable for approval was endorsed by V.Sayeed, Ph.D., Director, Division of Chemistry III on 6/19/14. Review of DMF updates has also bee completed (per e-mail dated 6/20/14 from Kevin Denny, RPM).

OGD Office Management Evaluation

5. Peter Rickman **Date 6/23/14**
Director, DLPS **Initials rlw/for**

Para.IV Patent Cert: Yes☐ ☐ ☐ No☐
Pending Legal Action: Yes☐ ☐ No☐
Petition: Yes☐ No☐
Entered to APTrack database ☐
GDUFA User Fee Obligation Status Met☐ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Bioequivalence waiver granted under 21 CFR 320.24(b)(6). Current Draft Guidance (/2012) for this drug product provides for in vitro option to establish bioequivalence. BE based upon in vitro Quantitative Capsule Rupture Test (QCRT) to assure equivalent release of the API from both RLD and Par's drug products. Par also submitted fasting and non-fasting studies, but the data from these studies was considered supportive of the BE determination. Office-level bio endorsed 3/7/14, 3/25/14.

Final-printed labeling (FPL) found acceptable for approval 6/5/14, as endorsed 6/6/14. No REMS is required.

CMC found acceptable for approval (Chemistry Review #4 - Addendum #1) 6/19/14.

OR

6. Robert L. West **Date 6/23/14**
Deputy Director, OGD **Initials RLWest**

Para.IV Patent Cert: Yes☒ ☐ ☐ No☐
Pending Legal Action: Yes☐ ☐ No☒
Petition: Yes☒ No☐
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met☒ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 1/21/14 (Verified 6/23/14). No "OAI" Alerts noted.

Par provided a paragraph IV certification to the '667 patent, and was sued within the 45-day period. Although Par lost the patent litigation at the district court level, Par prevailed at the appellate Court level with a finding of invalidity of the '667 patent. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

Par may be eligible for "shared" 180-day exclusivity for this drug product. However, Par did not receive a tentative approval within the 30-month period. Thus, as was done for Teva's approval under ANDA 91-028 on 4/17/14, the "punt" language with respect to 180-day exclusivity will also appear in Par's approval letter.

At present, there is a pending Citizen Petition from Jason Williams (FDA-2014-P-0699) requesting a stay of action - no further approvals for Omega-3-Acid Ethyl Esters Capsules. This petition has been classified as a 505(q) petition with a due date of 10/20/14. A memorandum to the record has been prepared concluding that the ANDA may be approved prior to the agency's response to the C.P. (e.g., a delay in the approval of Par's ANDA is not necessary in order to protect the public health).

This ANDA is recommended for approval.

7. ***OGD Director Evaluation***

Kathleen Uhl

Comments: RLWest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs 6/23/14.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

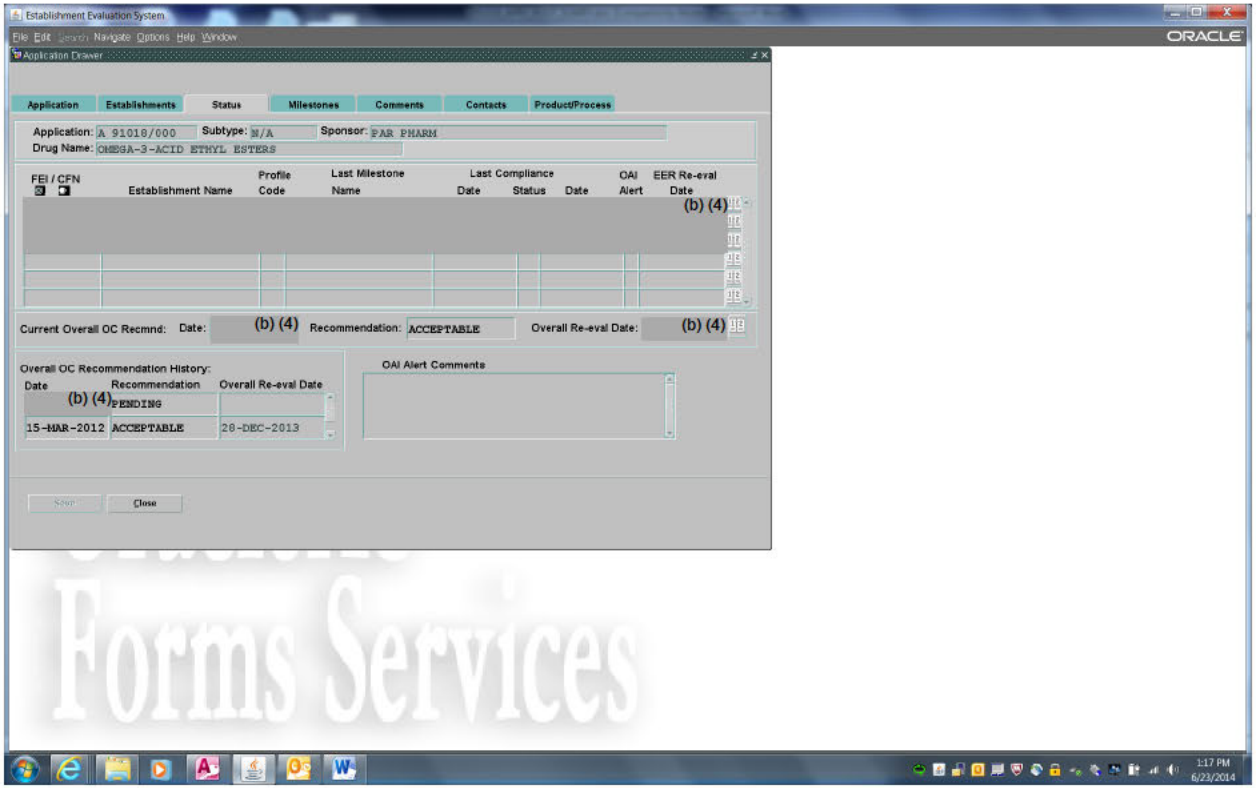
Comments:

8. Project Manager **Date 6/24/14**
Initials CO

Comments:

Check Communication and Routing Summary into DARRTS

EES DATA:


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product/Process
Application: A 91016/000
Subtype: N/A
Sponsor: PAR PHARM
Drug Name: OMEGA-3-ACID ETHYL ESTERS
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Compliance Date
Status
Date
OAI Alert
EER Re-eval Date
(b) (4)
Current Overall OC Recmnd:
Date:
(b) (4)
Recommendation:
ACCEPTABLE
Overall Re-eval Date:
(b) (4)
Overall OC Recommendation History:
Date
Recommendation
Overall Re-eval Date
(b) (4)
PENDING
15-MAR-2012
ACCEPTABLE
28-DEC-2013
OAI Alert Comments
Save
Close
Forms Services
1:17 PM
6/23/2014

Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 021654 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021654	001	5656667	Apr 10, 2017	Y	Y	U - 822	

Exclusivity Data

There is no unexpired exclusivity for this product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHINYELUM A OLELE
06/25/2014

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 23, 2014

FROM: Kathleen Uhl, M.D., Acting Director
Office of Generic Drugs

SUBJECT: Citizen Petition (FDA-2014-P-0699) and the Approvability of ANDA 091018

TO: ANDA 091018 – Par Pharmaceutical, Inc.

OVERVIEW

This memorandum addresses whether certain requests made in a citizen petition submitted by Jason Williams on May 22, 2014 (FDA-2014-P-0699) (Petition) affect the approval of abbreviated new drug application (ANDA) 091018 submitted by Par Pharmaceutical, Inc. (Par), which references Lovaza (omega-3 acid ethyl esters) (new drug application (NDA) 021654) as the reference listed drug (RLD). Specifically, the petitioner's requests related to Lovaza and any applications that reference it are that FDA: (1) not approve any ANDA or 505(b)(2) NDA that cites Lovaza as the RLD or listed drug until FDA takes actions requested in another citizen petition, FDA-2013-P-1612; and (2) add boxed warnings and require the distribution of Dear Health Care Provider (DHCP) letters regarding low-density lipoprotein cholesterol (LDL-C) increases in all mixed omega-3 formulations, including Lovaza.[1]

[1] Though the petitioner makes additional requests, this memorandum only addresses those requests that refer to Lovaza and any ANDAs or 505(b)(2) NDAs that reference it. For completeness, the requests are listed below (Petition at 1):

1. "[G]rant a stay of action" for two omega-3 acid ethyl ester products: (1) ANDA 091028, approved on April 7, 2014, and (2) NDA 204977, approved on April 23, 2014, "due to public safety concerns";

2. Not accept or approve any "ANDA or 505(B)(1) or 505(B)(2) applications" for the "RLD drugs Lovaza or Vascepa [(icosapent ethyl) (NDA 202057)] until the Secretary/Commissioner takes actions requested from Citizen Petition FDA-2013-P-1612-0073";

3. Add to the labeling of Epanova (omega 3 carboxylic acids) (NDA 205060) "the same Warnings and Precautions as other mixed Omega 3's. Currently Epanova label[ing] doesn't contain 5.3 Atrial Fibrillation precautions"; and

4. Add boxed warnings and require the distribution of Dear Health Care Provider (DHCP) letters on the "dangerous [low-density lipoprotein cholesterol (LDL-C)] increases in all mixed omega 3 formulations including Lovaza, Omega-3 [ethyl esters], Omtryg, and Epanova."

Par's ANDA was filed on November 10, 2008. After completing the review of Par's ANDA, OGD concludes that this ANDA is ready for final approval. Based on the applicable statutes, regulations, and policies and a review of the Petition, the Food and Drug Administration (FDA or the Agency) concludes that a delay in approving any ANDA or 505(b)(2) NDA that cites Lovaza as the RLD or listed drug is not necessary to protect the public health, notwithstanding the issues raised in the Petition.[2] The Agency's analysis is discussed below.

ANALYSIS

The petitioner asks FDA to condition the approval of any ANDA or 505(b)(2) NDA[3] citing Lovaza (or Vascepa) as the RLD or listed drug upon a resolution of a citizen petition concerning the decision to rescind a special protocol assessment (SPA) agreement concerning the ANCHOR study for Amarin Pharma, Inc.'s (Amarin) supplemental new drug application (sNDA) for Vascepa (Petition at 1).[4] EPA Drug Initiative and 25 petitioners filed the same citizen petition (Docket No. FDA-2013-P-1612) asking FDA to overturn the decision by CDER's Division of Metabolism and Endocrinology Products (DMEP) to rescind the ANCHOR SPA, and to delay the Prescription Drug User Fee Act date for supplemental NDA 202057/S-005 that concerns the approval of Vascepa for the ANCHOR indication. The ANCHOR SPA rescission decision, however, concerns a different drug (Vascepa) and a different application, and thus has no relevance to the acceptance, review, or approval of any ANDA or 505(b)(2) NDA citing Lovaza as the RLD or listed drug. Nor has the petitioner provided any valid scientific information or regulatory requirements to link the ANCHOR SPA rescission to such ANDAs or 505(b)(2) NDAs.

The petitioner also asks FDA to add a boxed warning and compel the distribution of DHCP letters "to warn of dangerous LDL increases in all mixed omega 3 formulations including Lovaza" (Petition at 1). FDA's regulations and guidance on prescription drug labeling explain when companies must add a boxed warning to a drug's labeling. The labeling regulations state that, "[c]ertain contraindications or serious warnings, particularly those that may lead to death or

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[2] See section 505(q)(1)(A) of the FD&C Act.

[3] The petitioner also requests that FDA not approve any 505(b)(1) NDAs that cite Lovaza or Vascepa as a listed drug. NDAs approved under section 505(b)(1) of the FD&C Act are supported entirely by full reports of investigations that are conducted by or for the applicant. An NDA that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug is usually submitted under section 505(b)(2) of the FD&C Act.

[4] The goal of the ANCHOR study was to evaluate the safety and effectiveness of Amarin's Vascepa for concomitant use with an inhibitor of HMG-CoA reductase (statin) to reduce TG, non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), LDL-C, total cholesterol (TC) and very-low-density lipoprotein cholesterol (VLDL-C) in adults with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent. A "Special Protocol-Agreement" letter was issued on July 6, 2009, on the ANCHOR study protocol. The protocol was later amended May 12, 2010, to revise the LDL-C and TG entry criteria. The results of the ANCHOR trial were submitted as an efficacy supplement to the Vascepa application (NDA 202057/S-005) on February 21, 2013, and publicly discussed at the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting on October 16, 2013. EMDAC members voted 9 to 2 against approval of Vascepa for co-administration with statin therapy for the treatment of patients with mixed dyslipidemia and CHD or CHD risk equivalent prior to the completion of REDUCE-IT, the ongoing Vascepa cardiovascular outcomes trial. (b) (4)

serious injury, may be required by the FDA to be presented in a box."[5] Further, in a guidance for industry,[6] FDA elaborates on the warnings that should be elevated to a boxed warning:

- "There is an adverse reaction so serious in proportion to the potential benefit from the drug . . . that it is essential that it be considered in assessing the risks and benefits of using the drug"; or

- "There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug . . ."; or

- "FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted . . ."[7]

The approved labeling for Lovaza and generic versions of Lovaza reflects FDA's determinations regarding the essential scientific information needed for the safe and effective use of these products, including whether particular information should be included in a boxed warning. Accordingly, such labeling already contains warnings and precautions on potential increases in LDL-C levels and on recommendations on the monitoring of these levels, but does not contain a boxed warning. Lovaza's labeling states: "In some patients, Lovaza increases LDL-C levels. LDL-C levels should be monitored periodically during therapy with Lovaza."[8] Despite the increases in LDL-C, FDA considers the benefit-risk profile of Lovaza to be acceptable when used to treat subjects with severe hypertriglyceridemia (triglyceride $\geq$ 500 mg/dL).[9] The petitioner did not submit any new scientific or clinical information in the Petition that would warrant a strengthening of the existing potential LDL-C warnings and precautions by adding a boxed warning. Therefore, at this time, FDA disagrees with the petitioner's request to add a boxed warning regarding potential LDL-C concerns to the labeling for Lovaza and any generic versions of Lovaza. DHCP letters are recommended to inform health care providers on new or updated information in the labeling.[10] Because FDA concludes that changes to the labeling of these omega-3 ethyl fatty acid products are not necessary at this time, DHCP letters are also unwarranted in this situation.

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[5] 21 CFR 201.57(c)(1).

[6] See Guidance for Industry, "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," October 2011, available at http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf.

[7] Id. at 11.

[8] Lovaza package insert, Section 5.1, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021654s041lbl.pdf.

[9] In patients with severe hypertriglyceridemia, the primary goal of lowering triglyceride levels is to reduce the risk of acute pancreatitis and not cardiovascular disease.

[10] See Guidance for Industry and FDA Staff, "Dear Health Care Provider Letters: Improving Communication of Important Safety Information," January 2014, available at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM233769.pdf.

The petitioner also claims that he is "aware of a very high [cardiovascular] population denied Vascepa coverage yet being approved for Lovaza / Generic Lovaza" (Petition at 2). The Agency assumes this claim relates to DMEP's decision to rescind the ANCHOR SPA for Vascepa while simultaneously permitting the labeling of Lovaza to retain clinical trial information on the very high triglyceride (200 to 499 mg/dL) population (Section 14.2 Other Clinical Experience), a similar population that was evaluated in the ANCHOR study. FDA approved a prior approval supplement for Lovaza on May 14, 2014, that removes Section 14.2 from Lovaza's labeling. Lovaza's labeling no longer references clinical studies of the drug in persons with triglyceride levels of 200 to 499 mg/dL. Par's proposed labeling for its ANDA does not contain the information under "Other Clinical Experience" that was removed from Lovaza's labeling. The petitioner's claim in this regard thus is moot.

Finally, the relative prevalence of use in the marketplace of Lovaza and the currently approved generic version of Lovaza (termed "dispensing information" by the petitioner) and/or market preferences (Petition at 2) are irrelevant to FDA's determination on the safety and/or effectiveness of Lovaza and any ANDAs or 505(b)(2) NDAs that reference Lovaza.

CONCLUSION

For the reasons described above, FDA concludes that a delay in approving Par's ANDA 091018 is not necessary to protect the public health, notwithstanding the issues raised in the Petition.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA L DOWNS
06/23/2014

KATHLEEN UHL
06/23/2014

COMPLETE RESPONSE

ANDA 091018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Par Pharmaceuticals Inc. TEL: 845-573-5780

ATTN: Julie Szozda FAX: 845-573-5795

FROM: Kevin Denny FDA CONTACT PHONE: 240-276-9667

Dear Madam:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 091018

COMPLETE RESPONSE

Par Pharmaceuticals Inc.
Attention: Julie Szozda
Submissions Manager, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated November 10, 2008, received November 10, 2008, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules USP, 1 gram.

We acknowledge receipt of your amendments dated May 22, September 30, 2009; February 9, February 12, March 2, May 5, August 24, August 26, 2010; September 28, December 7, 2011; June 25, November 1, 2013; February 18, February 19, February 27, and March 14, 2014.

The October 14, 2009, submission constituted a complete response to our March 10, 2009, action letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies

1. The drug master file # (b) (4) for Omega-3 acid ethyl esters is currently inadequate. The DMF holder, (b) (4) has been notified. Please do not respond to this letter until the DMF holder has informed you that they have responded to all the deficiencies. Please update your drug substance specifications in consultation with your DMF holder and provide updated methods and validations as applicable.

2. (b) (4)

3. (b) (4)

4.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your proposed (b) (4) of this review. Please acknowledge.

2. Please make all applicable changes to your drug product release/stability specifications per the Division of Bioequivalence recommendations.

BIOEQUIVALENCE

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

DISSOLUTION

The Division of Bioequivalence I (DB1) has completed its review of your submissions acknowledged on the coversheet and has no further questions at this time. We acknowledge that you will conduct the dissolution testing of your test product using the following FDA-recommended dissolution method and specifications:

Medium	4.0% Triton X-100 in 0.01 N HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)

Also, as mentioned in your submission, DB1 acknowledges that you will have an effective finished product/stability monograph in place prior to conducting the QCRT.

LABELING

Labeling Deficiencies determined on February 27, 2014, based on your submission dated February 19, 2014.

1. CONTAINER (120s)

   The container labels submitted on February 19, 2014 are blurry and difficult to read. Please revise and submit labels in final print in a text based PDF file instead of image based.

2. INSERT

   a. HIGHLIGHTS, Title: We encourage you to use upper case letter for the drug substance and lower case letter for the dosage form and route of administration.

   b. Revise "Omega-3" to read Omega-3-Acid ethyl esters" [2 occurrences (Heading in Table 1 and Table 2)].

   c. Inactive Ingredients: You listed the content of α-tocopherol to be 3.8 to 4.2 mg/capsule in the amendment dated 2/19/2014. However, in your response to the labeling deficiency dated 11/18/2009, you stated the following.

   Labeling comment:
   GENERAL COMMENT:
   We note that you do not have "α-tocopherol" listed as an inactive ingredient. However, in 2.3.P.5(original submission), the content of α-tocopherol is stated as (b)(4) mg/capsule. Please explain this discrepancy.

   Firm's Response
   The content of "α-tocopherol" was inadvertently omitted from the listing of inactive ingredients in the insert. The content of α-tocopherol as (b)(4) mg/capsule is now listed as an inactive ingredient in the insert

   Please explain this discrepancy.

3. PATIENT INFORMATION LEAFLET

   a. Please include the dosage form in the established name when reference is made to the drug product.

   b. Refer to INSERT comment 2(c).

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY /LABELING

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Chinyelum Olele, Regulatory Project Manager, at (240) 276-9778

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

ROBERT L WEST

03/28/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

BIOEQUIVALENCE AMENDMENT

ANDA 091018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Par Pharmaceuticals Inc.

TEL: 845- 573- 5780

ATTN: Julie Szozda

FAX: 845- 573- 5795

FROM: Chinyelum Olele

FDA CONTACT PHONE: 240-276-9778

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on November 10, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3 Acid Ethyl Esters Capsules, 1 gram.

Reference is also made to the amendments dated Novemeber 1, 2013, February 18, 2014, and February 27, 2014.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 091018

APPLICANT: Par Pharmaceuticals Inc.

DRUG PRODUCT: Omega-3 Acid Ethyl Esters Capsules, 1 gram

The Division of Bioequivalence I (DBI) has completed its review of the drug release testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver request will be conducted later. The following deficiency has been identified:

1. Your quantitative capsule rupture testing (QCRT) data, using the method stated below, are acceptable. However, your proposed specifications of "NLT (b) (4)% (Q) in (b) (4) minutes" for both DHAee and EPAee are not acceptable. Based on the submitted data, DBI recommends the following QCRT method and specifications for release and stability testing of your test product:

Medium	4.0% Triton X-100 in 0.01 N HCl with pepsin (120k/L)
Volume	900 mL
Temperature	37°C ± 0.5°C
USP Apparatus	I (basket, mesh size 40)
Rotational Speed	100 rpm
Specification	NLT (b) (4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 300 minutes (5 hours)

The following comment is for future submissions of QCRT:

2. Your Finished Product/Stability Analytical Procedure SOP #fs-019-011 for the above QCRT was effective 10/29/2013, while the QCR testing was conducted in 09/2013. In future submissions, please be advised that an effective SOP should be in place prior to conducting the QCRT.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

DALE P CONNER
03/07/2014

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 091018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Par Pharmaceuticals Inc.

TEL: (845) 573-5780

ATTN: Julie Szozda

FAX: (845) 573-5795

FROM: Chinyelum Olele

FDA CONTACT PHONE: (240) 276-9778

Dear Madam:

This communication is in reference to your abbreviated new drug application (ANDA) dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-acid ethyl esters Capsules, 1 gram.

Reference is also made to your amendment dated 2/18/2014.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
BIOEQUIVALENCE

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Chinyelum Olele at (240) 276-9778.

We have completed our review, as amended, and have the following comments:

BIOEQUIVALENCE

Re: Quantitative Capsule Rupture (QCR) testing method

For your proposed QCRT method with basket, you did not specify the mesh size for the basket. If you did not use the USP 40-mesh basket, please provide justification for not using the USP mesh size, and full description of the mesh basket used in your proposed method for evaluation.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/26/2014

FDA FAX

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: PAR PHARMACEUTICAL INC TEL: 845-573-5673

ATTN: Janis A. Picurro FAX: 845-573-5795

This facsimile is in reference to your abbreviated new drug application(s), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

DATE: 2/9/2014

TO: PAR PHARMACEUTICAL INC

ATTN: Janis A. Picurro

E-Mail: janis.picurro@parpharm.com

FAX: 845-573-5795

RE: Update summary of filed and pending original ANDA(s)

Dear Sir or Madam:

The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is providing you with this one-time communication on the status of your filed and pending original abbreviated new drug application(s) (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act. OGD is providing these updates as an interim measure to help applicants assess the status of their current submissions as we transition towards predictable goal times pursuant to the Generic Drug User Fee Amendments of 2012 (GDUFA).

Your status update is limited to available review information as of January 29, 2014. Any additional information regarding your ANDA collected after this date is neither considered nor provided. Furthermore, your ANDA status is subsequently subject to revision pending additional information or concerns raised by any of the discipline reviews (bioequivalence, clinical, chemistry, microbiology, labeling, facility), other unforeseen legal, scientific or regulatory issues, or inspectional results, which can also impact the status or ability to issue a complete response. Any applicable fees can also affect the status of your ANDA.

OGD is providing your ANDA status update in the attached chart with a list of applicable acronyms. The chart only contains current information regarding discipline review and does not forecast if and when OGD will issue a complete response, tentative approval, or final approval letter.

Please do not respond to this communication by asking FDA or your Regulatory Project Manager for additional or more detailed information. This is a one-time communication intended to assist you to ascertain the current status of submissions. It is not feasible for us to respond to a high volume of follow up inquiries.

Sincerely yours,

CAPT Aaron W. Sigler, USPHS
Chief, Review Support Branch

ANDA	DRUG NAME	CHEM	BIO	MICRO	LABEL	CLINICAL	FACILITY
91018	OMEGA-3-ACID ETHYL ESTERS CAPSULES	UR	UR	NA	IQ	NA	AC
							(b) (4)
203918	SODIUM PHENYLBUTYRATE POWDER						(b) (4)
203976	COLCHICINE. TABLETS						

CHART ACRONYMS

Column Headings

ANDA - The application number for your Abbreviated New Drug Application
DRUG NAME - The official filed name of the drug associated with the ANDA number
CHEM - Product Quality Chemistry Review
BIO - Bioequivalence Review, typically including OSI, if applicable
MICRO - Microbiology Review
LABEL - Labeling Review
CLINICAL - Clinical Review
FACILITY - Overall Facility inspections summary. All facilities must be acceptable at the time of 29 JAN 14 in order to warrant an adequate notation. If one of more facility is not acceptable then the FACILITY column will be marked as such. OSI information is not considered.

Discipline Notations

IQ - Inadequate. This particular discipline is currently found to be inadequate.

AQ - Adequate. This particular discipline was found to be adequate when the information was gathered for this communication.

UR - Under Review. This particular discipline is currently assigned OR under review with the discipline team.

NR -Not Reviewed. This particular discipline is either currently not under review or assigned.

NA - Not applicable. This particular discipline is not required for the approval of this ANDA.

Facility Notations

PN - Pending, i.e., one or more facilities have been inspected and are pending an outcome.

AC - All facilities are acceptable at the time of this publication.

*Please note that you may receive your updates in multiple communications over time, based on the number of ANDAs pending in OGD.

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/s/

SIMON S ENG on behalf of AARON W SIGLER
02/10/2014

EASILY CORRECTABLE DEFICIENCY EMAIL

ANDA 091018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Par Pharmaceutical Inc. TEL: (845) 573-5780

ATTN: Julia Szozda FAX: (845) 573-5795

FROM: Robert Gaines FDA CONTACT PHONE: (240) 276-8495

Dear Madam:

This communication is in reference to your abbreviated new drug application (ANDA) dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Ester Capsule USP, 1 gram.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFFICIENCY
LABELING

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Robert Gaines at (240) 276-8495.

We have completed our review, as amended, and have the following comments:

Labeling Deficiencies determined on August 13, 2013 based on your submission dated February 9, 2010 and August 24, 2010.

1. GENERAL COMMENT:
   This product is the subject of a USP monograph. We encourage you to add "USP" to the established name in the container labels and insert labeling.

2. CONTAINER
   a. Please revise the expression of strength to read "1 gram*" add an asterisk immediately before the "*Each capsule contains…" statement on the side panel.

   b. Add "Protect from light" to the storage statement.

   c. Add "Swallow capsules whole" on the principal display panel.

   d. Please decrease the prominence of the net quantity statement.

3. PHYSICIAN INSERT
   a. GENERAL COMMENTS:
      i. Due to changes in the insert labeling for the reference listed drug Lovaza® (omega-3-acid ethyl esters) Capsules by GlaxoSmithKline, (NDA 021654/S-039) approved September 11, 2013, please revise your labeling to be in accordance with the reference listed drug labeling.

      ii. The Agency recommends two-column format for the "HIGHLIGHTS" and "CONTENTS" sections. Please revise.

   b. HIGHLIGHTS, Title: Please also include the route of administration (refer to 21 CFR 201.57 (a)(2)).

   c. Please insert a horizontal line to separate the information in HIGHLIGHTS OF PRESCRIBING INFORMATION section, from the FULL PRESCRIBING INFORMATION: CONTENTS* section and also the FULL PRESCRIBING INFORMATION section (refer to 21 CFR 201.57 (d)(2)).

   d. DESCRIPTION: Please confirm if the following statement accurately reflects your drug product: These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA- approximately 465 mg) and docosahexaenoic acid (DHA- approximately 375 mg).

   e. HOW SUPPLIED/STORAGE AND HANDLING: Please add "Protect from light" to the storage statement.

4. PATIENT INFORMATION LEAFLET
   a. Please provide the stand-alone patient information leaflet for our review.

   b. Please ensure that your leaflet is in accordance with the RLD approved on September 11, 2013.

5. SPL
   a. In the data elements, revise the strength to read “Omega-3-Acid Ethyl Esters, 900 mg” rather than “Omega-3-Acid Ethyl Esters, 1 g.”

   b. Please update to be in accordance with the RLD approved on September 11, 2013.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug’s labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

BETTY B TURNER
02/07/2014
for Wm Peter Rickman

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 091018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Par Pharmaceuticals Inc.

TEL: (845) 573-5780

ATTN: Julie Szozda

FAX: (845) 573-5795

FROM: Robert Gaines

FDA CONTACT PHONE: (240) 276-8495

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-acid ethyl esters Capsules, 1 gram.

Reference is also made to your amendments dated November 1, 2013 and September 30, 2009.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
BIOEQUIVALENCE

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Robert Gaines at (240) 276-8495.

We have completed our review, as amended, and have the following comments:

BIOEQUIVALENCE

Re: Quantitative Capsule Rupture (QCR) testing study reports

1. According to the amendment dated 11/01/2013, you chose QCR method using basket for finished drug release. In your QCR amendment dated 09/30/2009, you had the following statements: *'the first actual dissolution using a* [redacted] ***All further experiments were run using Apparatus 2, paddles and helix sinkers'***. Please explain your latest proposal of using basket in the QCR testing in relation to the earlier statements above about the inappropriateness of the basket. Please provide supporting data with your response.

2. You did not provide the Certificate of Analysis (CoA) for the reference listed drug product, Smithkline Beecham's Lovaza® Capsules, lot #IZP0924, used in the QCR testing with flow-through and basket methods. Please submit the information.

3. You did not provide storage conditions of the test (lot # E041301) and reference (lot #1ZP0924) products used in the QCR testing with flow-through and basket methods (i.e., how the test lots were stored between the manufacturing date and testing date; similarly, how the reference lots were stored following acquisition). Please provide the storage conditions for the products used in the QCR testing.

4. For the validation of the assay method used in the QCR testing with basket, you did not submit the method Standard Operation Procedure (SOP) or method validation SOP. Please provide the relevant SOPs.

5. Your QCR testing using the basket method was conducted at Par Pharmaceutical Inc., One Ram Ridge Road, Spring Valley, NY 10977. You did not provide the detailed address (street number, street name, city, state and country) where the method validation of the QCR testing was performed in the method validation report (reports # [redacted]). Please provide this information. The suitability of the QCR testing method should be validated at the same site where QCR testing is conducted. Therefore, if the method validation site is different from the QCR testing site, you should either validate the QCR method at the QCR testing site or provide the method transfer report between sites.

6. In your QCR testing validation report using the basket method (reports # [redacted], located at Module 3.2.P.5.3), you did not conduct accuracy or intermediate precision studies. Please provide results for these studies.

7. For the validation of the assay method used in the QCR testing with flow-through cell, you did not submit the method SOP or method validation SOP. Please provide the relevant SOPs.

8. Your QCR testing using the flow-through cell was conducted at Par Pharmaceutical Inc., One Ram Ridge Road, Spring Valley, NY 10977. You did not provide the detailed address (street number, street name, city, state and country) where the method validation of the QCR testing was performed in the method validation report (reports # [redacted]). Please provide this information. The suitability of the QCR testing method should be validated at the same site where QCR testing is conducted. Therefore, if the method validation site is different from the QCR testing site, you should either validate the QCR method at the QCR testing site or provide the method transfer report between sites.

9. In your QCR validation report using the flow-through cell method (reports # [redacted], located at Module 3.2.P.5.3), you did not conduct accuracy study. In addition, you used [redacted] filter in the QCR testing but did not conduct filter validation study. Please provide results for these studies.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/05/2014

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 091018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Par Pharmaceutical, Inc. TEL: (845) 573-5780

ATTN: Julia Szozda FAX: (845) 573-5795

FROM: Sherry Chang FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to your abbreviated new drug application (ANDA) dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-acid ethyl esters Capsules, 1 gram.

Reference is also made to your amendments dated August 26, 2010, May 5, 2010, September 30, 2009, and December 7, 2011

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies with an "***AMENDMENT/EASILY CORRECTABLE DEFICIENCY***" within ten (10) business days.

If you do not submit a complete response within ten (10) business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments. In addition, please notify the Project Manager listed below.

A partial response to this fax will not be processed as an amendment and will not start a review. Please submit official archival copies of your response to the ANDA. Please notify the above Project Manager when your amendment has been submitted.

If you have questions regarding these deficiencies please contact the Project Manager, Sherry Chang at (240) 276-8782.

SPECIAL INSTRUCTIONS:

We are reviewing this ANDA, as amended, and have the following comments:

BIOEQUIVALENCE

In order for the Division of Bioequivalence I (DBI) to evaluate your test formulation, please provide concentrations for all ingredients in the test formulation in the following detailed format:

A. ACTIVE PHARMACEUTICAL INGREDIENT:

1. Most abundant components: EPAee and DHAee:
   i) Eicosapentaenoic acid ethyl ester (EPAee; C20:5 n-3): Concentration in mg/g unit
   ii) Docosahexaenoic acid ethyl ester (DHAee; C22:6 n-3): Concentration in mg/g unit
   iii) Sum of EPAee and DHAee: Concentration in mg/g unit
   iv) Total omega-3 acid ethyl esters: Concentration in %w/w unit

2. Additional components present at greater than or equal to 10 mg/g encapsulated oil: SDAee, HPAee, DPAee:
   i) Moroctic acid ethyl ester (SDAee; C18:4 n-3): Concentration in mg/g unit
   ii) Heneicosapentaenoic acid ethyl ester (HPAee; C21:5 n-3): Concentration in mg/g unit
   iii) Docosapentaenoic (Clupanodonic) acid ethyl ester (DPAee; C22:5 n-3): Concentration in mg/g unit
   iv) Please indicate the presence or absence of: Eicosatetraenoic acid ethyl ester (ETAee; C20:4 n-3)

Please provide the concentration (in mg/g unit), if appropriate.

B. INACTIVE INGREDIENTS:

1. Alpha-tocopherol: Concentration in mg/g unit
2. Please indicate the presence or absence of: Soybean oil

Please provide the concentration (in mg/g unit), if appropriate.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

HOAINHON N CARAMENICO on behalf of DALE P CONNER
06/12/2013

From: Gaines, Robert
To: Chang, Sherry
Cc: Nguyen, Hoainhon T
Subject: RE: ANDA 091018 Original BE Review Easily Correctable Deficiencies
Date: Tuesday, June 11, 2013 12:21:35 PM

Looks good.

From: Chang, Sherry
Sent: Tuesday, June 11, 2013 12:06 PM
To: Gaines, Robert
Cc: Nguyen, Hoainhon T
Subject: ANDA 091018 Original BE Review Easily Correctable Deficiencies

Hello Bob,

Thank you for yesterday.

For clarification, please view the attached ECD and confirm the following points:

1. The PM listed in this ECD cover sheet (page 1): Sherry Chang
2. The content of ECD letter (page 2): Bioequivalence comments (Discipline specific)
3. The signature (page 2): Dr. Dale Conner (Division specific Director)

<< File: ANDA 091018 Bio ECD 6-11-13.doc >>

Thank you,

Sherry Chang, Pharm.D.

Project Manager, Branch II
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SHERRY CHANG
06/12/2013

QUALITY DEFICIENCY - MINOR

ANDA 091018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Par Pharmaceutical, Inc. TEL: 845- 425-7100

ATTN: Karen Rocco FAX: 845- 639- 5201

FROM: Leigh Ann Sears FDA CONTACT PHONE: (240) 276-8453

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules, 1 g.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

III. List of Deficiencies to be communicated:

ANDA: 091018
APPLICANT: Par Pharmaceutical, Inc.
DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules

The deficiencies presented below represent a Minor deficiency.

A. Deficiencies:

(b) (4)

Upon receiving the above requested data a complete CMC review of the application will be undertaken.

Sincerely yours,

{See appended electronic signature}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEIGH A SEARS
06/07/2011

LAXMA R NAGAVELLI
06/07/2011
Signed for Vilayat A Sayeed, PhD

BIOEQUIVALENCE AMENDMENT

ANDA 091018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Par Pharmaceutical, Inc. TEL: (845) 573-5780

ATTN: Julie Szozda FAX: (845) 573-5795

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on November 10, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules, 1 gram.

Reference is also made to your amendment dated May 5, 2010.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request **Bioequivalence Dissolution Acknowledgement**

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 091018

APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

Your dissolution testing data comparing your product, Omega-3-Acid Ethyl Esters Capsules, 1 g, with the reference product SmithKline's Lovaza® Capsules, 1 g, using your proposed Method I are acceptable. However, your proposed specification for this proposed method I is not acceptable. Based on the data submitted, the DBE recommends more appropriate specification below.

Compared with your proposed Method I, your proposed Method II is not considered sufficiently discriminatory, and therefore, not acceptable.

Please acknowledge your acceptance of the following dissolution method and specification:

Medium	5% Triton X-100 in water with 1% pancreatin
Volume	900 mL
Temperature	37°C
USP Apparatus	II (paddles)
Rotational Speed	75 rpm
Specification	NLT (b)(4)% (Q) of labeled amount of each EPA and DHA in the dosage form is dissolved in 60 minutes

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91018	ORIG-1	PAR PHARMACEUTICAL	OMEGA-3-ACID ETHYL ESTERS

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/s/

DALE P CONNER
08/17/2010

BIOEQUIVALENCE AMENDMENT

ANDA 091018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Par Pharmaceutical, Inc. TEL: (845) 573-5780

ATTN: Julie Szozda FAX: (845) 573-5795

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on November 10, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules, 1 gram.

Reference is also made to your amendment dated September 30, 2009.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 091018

APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The Division of Bioequivalence (DBE) has completed its review of the disintegration and quantitative rupture testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiencies have been identified:

As requested, you have explored different *in vitro* testing conditions in developing a quantitative rupture test method for the test product. Your method development report demonstrated that testing in (b) (4) media with the surfactants of (b) (4) On the other hand, the results of your testing in the aqueous media with different concentrations of the surfactant Triton X-100 have shown to be more promising. However, the paddle speed of 150 rpm for this latter method was excessive. In addition, the testing results showed that the capsules were either intact (with almost 0% dispersed) or completely ruptured (with almost 100% dispersed) during the testing. It appeared that the high paddle speed may have caused rupture of the capsules by sudden contact of the capsules with the paddle shaft, resulting in almost 100% dispersion following no (almost 0%) dispersion at the previous sampling times.

1. Therefore, the DBE recommends that you further modify the testing method with the aqueous media of Triton X-100 to achieve more gradual rupture and dispersion process, using (b) (4) concentrations of Triton X-100 concentrations and/or (b) (4) **agitation** speeds, as suggested below:

Medium:	Water + (**5% Triton X-100, or 8% Triton X-100, or 10% Triton X-100**)
Apparatus:	USP apparatus II (paddle)
Speed:	**50 rpm, or 75 rpm, or 100 rpm**
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

If necessary, you may try varying the media volume.

2. Alternatively, you may consider using USP Apparatus IV (flow-through Cell) or USP Apparatus III (reciprocating cylinder) instead of Apparatus II (paddle) to avoid practical problems such as the oil floating to the surface of the medium and concentrating around the shaft. If all capsules tested rupture in less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. Please refer to the reference article, *USP PF Charter 35 (4) Stimuli to the Revision Process: Liquid-filled Gelatin Capsules* for helpful considerations in developing an *in vitro* testing method for similar dosage forms. As advised in this article, a quantitative capsule rupture test characterizes the capsule shell rupture process as well as the dispersion of the active ingredient in the surrounding medium, and thus is a more appropriate way to describe the drug releasing process from its formulation. The DBE currently recommend quantitative capsule rupture test be performed for all soft gel capsule products in which the Active Pharmaceutical Ingredient (API) is dissolved in an oily matrix.

   For the requested quantitative capsule rupture testing above, please use 12 units each of your Omega-3-Acid Ethyl Esters Capsules, 1 g, and the reference listed drug product, Lovaza®, 1 g, and provide the data for individual units as well as mean data, with CV% and range, for each test.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91018	ORIG-1	PAR PHARMACEUTICAL INC	OMEGA-3-ACID ETHYL ESTERS

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/s/

DALE P CONNER
02/17/2010

Telephone Fax

ANDA 91-018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986

TO: Par Pharmaceutical, Inc. TEL: 845-639-5128

ATTN: Julie Szozda FAX: 845-639-5201

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega- 3 Acid Ethyl Esters Capsules, 1 gram

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-018 Date of Submission: May 22, 2009
Applicant's Name: Par Pharmaceutical Inc.
Established Name: Omega 3-Acid Ethyl Esters Capsule, 1 gram

Labeling Deficiencies:

1. **GENERAL COMMENT:**

We note that you do not have "α-tocopherol" listed as an inactive ingredient. However, in 2.3.P.5-(original submission), the content of α-tocopherol is stated as (b) (4) mg/capsule. Please explain this discrepancy.

2. **CONTAINER**: (60's, 120's)

Acceptable in final print.

3. **INSERT:**

Please revise your insert in accordance to the most recently approved RLD labeling (21654/S-022; approved 9/16/09). We refer you to Drugs@FDA website.

4. **PATIENT PACKAGE INSERT:**

Please see INSERT comment.

Submit final printed labeling electronically. We refer you to the http://www.fda.gov/oc/datacouncil/spl.html website for guidance.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the most recently approved RLD labeling with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91018	ORIG-1	PAR PHARMACEUTICAL	OMEGA-3-ACID ETHYL ESTERS

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/s/

JOHN F GRACE
11/18/2009
for Wm Peter Rickman

BIOEQUIVALENCE AMENDMENT

ANDA 91-018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Par Pharmaceutical Inc. TEL: 845- 639- 5152

ATTN: Karen Rocco FAX: 845- 639- 5201

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on November 10, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules, 1 gram.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **two** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 91-018

APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 gram

The Division of Bioequivalence (DBE) has completed its review of the disintegration testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiencies have been identified:

1. Your disintegration testing is incomplete. Please submit the individual tablet data (disintegration times of the individual tablets) for the test and reference products. Additionally, a summary of the disintegration testing data should be provided in the eCTD table and should include the relevant information such as the apparatus, volume of the medium, testing dates, and batch numbers of the test and reference products used in testing.

2. Currently, the DBE recommends a quantitative rupture test method be used to evaluate the *in vitro* performance of the drug product. Please develop your own quantitative capsule rupture method which should be discriminating to detect potential differences between the test and reference products. Please measure drug release of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA). You may consider trying the following method:

Apparatus:	USP apparatus I (basket)
Speed:	100 rpm
Medium:	Water with a low concentration of surfactant
Volume:	900 mL
Sampling:	Once every 15 minutes until at least 80% of the labeled amount of Eicosapentaenoic acid (EPA) and Docosahecaenoic acid (DHA) is dispersed in the media

   Number of Units Tested: 12

   If necessary, we suggest you try varying the medium volume, changing the rotational speed, adjusting the concentration of surfactant used, and/or using USP Apparatus II (paddles) instead of Apparatus I. If all capsules tested rupture in

less than one hour, it may be necessary to sample more frequently to adequately characterize the capsule rupture rate and profile. Please provide individual capsule data as well as the test summary data such as mean, range and % coefficient of variation (CV) at each time point. The summary of the quantitative rupture testing data should also be provided in eCTD-formatted tables.

3. Please provide long term storage stability data of free eicosapentaenoic acid and free docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for free eicosapentaenoic acid and free docosahexaenoic acid assay, which is at least 75 days. Please also provide long term storage stability data of eicosapentaenoic acid and docosahexaenoic acid in frozen plasma to cover the maximum storage time of the study samples for eicosapentaenoic acid and docosahexaenoic acid assay, which is at least 61 days.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dale Conner

5/6/2009 02:20:15 PM

Telephone Fax

ANDA 91-018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986

TO: Par Pharmaceutical, Inc. TEL: 845-639-5128

ATTN: Julie Szozda FAX: 845-639-5201

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega- 3 Acid Ethyl Esters Capsules, 1 gram

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-018 Date of Submission: November 10, 2008
Applicant's Name: Par Pharmaceutical Inc.
Established Name: Omega 3-Acid Ethyl Esters Capsule, 1 gram

Labeling Deficiencies:

1. **CONTAINER**: (60's, 120's)
   a. The manufacturer of this product is Emcure, yet there is no mention of Emcure on the labels. According to 21 CFR 201.1(h)(2), "The appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer of the product. That representation is false and misleading, and the drug product is misbranded under section 502(a) of the act, if the person is not the manufacturer of the product in accordance to this section". Please revise your labels by adding "Distributed by Par..." or "Manufactured by Emcure..."

   b. We encourage adding the statement "Pharmacist: please dispense with patient package insert".

2. **INSERT:**
   a. Please add "Rx only" to appear directly below the title of the insert.

   b. DESCRIPTION: Please add the components of the (b) (4) to your list of inactive ingredients.

   c. CLINICAL STUDIES: The subjection "Very High Triglycerides: (b) (4) from your proposed labeling. Please refer to the RLD.

   d. PRECAUTIONS: Revise the "Pregnancy" subsection to read:

   (b) (4)

   Pregnancy Category C

   e. In section 2.3.P.5 of the QOS, the gelatin capsules were imprinted with "019" while the HOW SUPPLIED section described the capsules imprinted with "P019". Please clarify.

3. **PATIENT PACKAGE INSERT:**
   Please see INSERT comment b.

Submit final printed labeling electronically. We refer you to the http://www.fda.gov/oc/datacouncil/spl.html website for guidance.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
4/21/2009 12:06:47 PM
for Wm Peter Rickman

COMPLETE RESPONSE -- MAJOR

ANDA 91-018

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Par Pharmaceutical, Inc. TEL: (845) 639-5128

ATTN: Julie Szozda FAX: (845) 639-5201

FROM: Jeanne Skanchy FDA CONTACT PHONE: (240) 276-8467

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 10, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omega-3-Acid Ethyl Esters Capsules, 1 g.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91-018 APPLICANT: Par Pharmaceutical, Inc.

DRUG PRODUCT: Omega-3-Acid Ethyl Esters Capsules, 1 g

The deficiencies presented below represent MAJOR deficiencies:

A. Deficiencies:

(b) (4)

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Iser
3/10/2009 11:51:01 AM
signed for V. Sayeed

Memo to File

Date: 3/10/2009

To: ANDAs 90-973, 91-018 and 91-028
Omega 3 Acid Ethyl Ester Capsules, 1.0 gram
ANDA submissions (filed)

From: Robert Iser, Team Leader, CMC Review Team 12
RE: Major Amendment

After discussion with the Team, Division, Regulatory Support, and Science Group, it was decided that due to insufficient characterization of the active, as compared to the current RLD, all sponsors will receive a major amendment letter without a CMC review of the submitted ANDA or associated DMF(s).

The letter text will be as follows:

The next review cycle will include a CMC review of the response to the above request and the previously submitted information, as applicable, as well as the associated DMF(s).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Iser

3/10/2009 08:06:05 AM

CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-018

Par Pharmaceutical, Inc.
Attention: Julie Szozda
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated January 9, 2009 and your correspondence dated January 12, 2009.

NAME OF DRUG: Omega-3-Acid Ethyl Esters Capsule, 1 g

DATE OF APPLICATION: November 10, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 10, 2008

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8419.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeanne Skanchy
Project Manager
240-276-8467

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Shimer
3/9/2009 10:49:06 AM
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 91-018 **FIRM NAME**: PAR PHARMACEUTICAL INC.

PIV: YES **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: OMEGA 3-ACID ETHYL ESTERS

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

DOSAGE FORM: CAPSULES, 1 GRAM
Random Queue: 12
Chem Team Leader: Robert Iser Chem PM: Jeanne Skanchy Labeling Reviewer: Ann Vu
Bio PM: Lizzie Sanchez (Acting PM)

Letter Date: NOVEMBER 10, 2008 **Received Date**: NOVEMBER 10, 2008

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 3031600 LIPID ALTERING AGENTS

Archival copy: CTD FORMAT PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Iain Margand	**Recommendation:**
Date 1/13/2009	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

ADDITIONAL COMMENTS REGARDING THE ANDA:

*****See Bio First Generic Filing Review below*****

1/9/2009:

Requested a revised FDA 3674 form with Box "B" checked in section nine instead of Box "A".

Requested a cGMP certification from the (b) (4)

Requested a (b) (4)

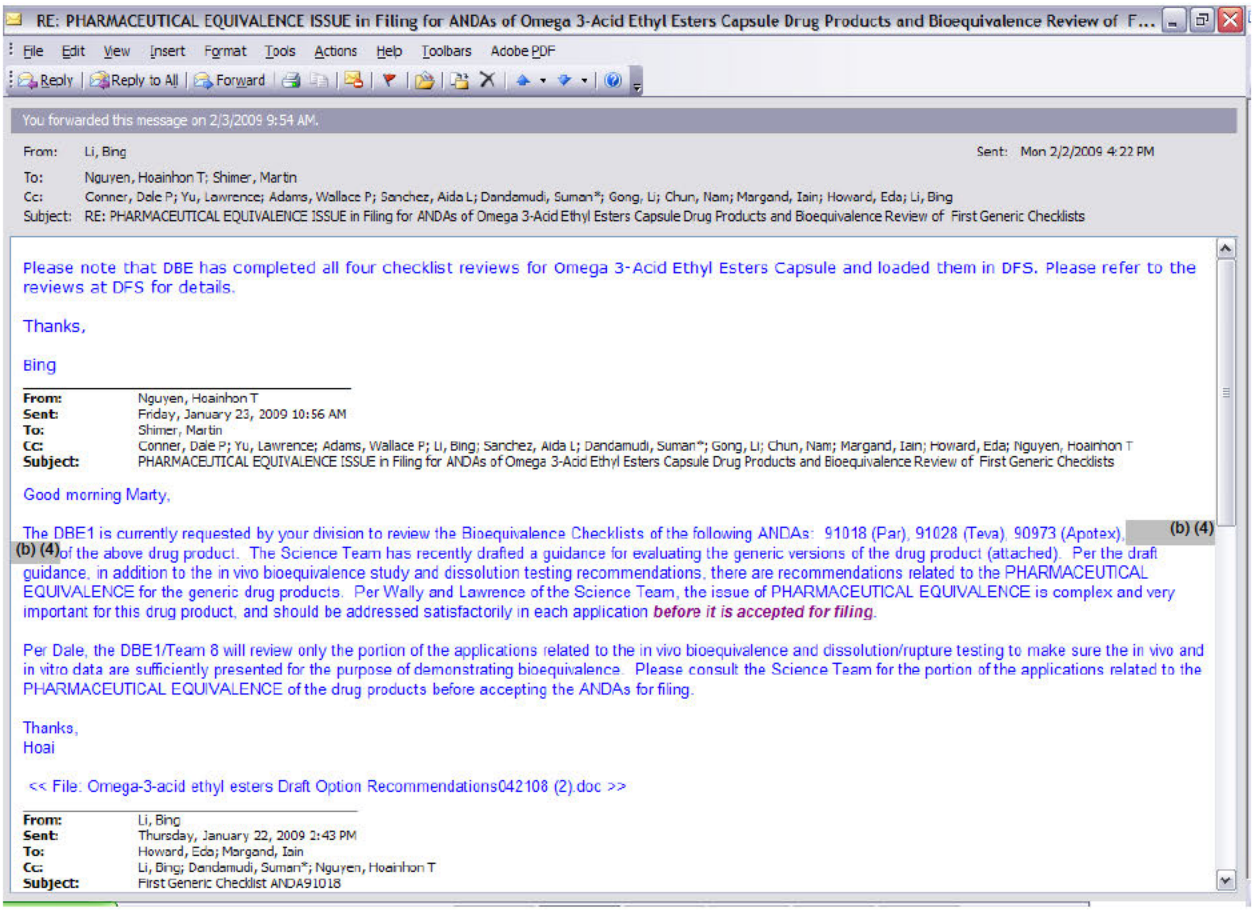
Requested clarification on patent certification to the '594 patent. Firm has filed a PIV certification to the patent which expires 8/4/2009. However, they also state they will not market the product until after the expiration of the M-64 exclusivity which expires 6/12/2010.

1/13/09:

Requested information received via fax and is acceptable. Firm has changed patent certification for the '594 patent from PIV to PIII.

****Initially there had been discussion to Refuse Omega-3 applications based on the potential for Pharmaceutical Equivalence issues that may arise with this product. However, a decision has been made to allow the applications to be filed and the PE issue will become a review issue.**

Contact: Karen Rocco 845-639-5152



RE: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of F...

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You forwarded this message on 2/3/2009 9:54 AM.

From: Li, Bing Sent: Mon 2/2/2009 4:22 PM

To: Nguyen, Hoainhon T; Shimer, Martin

Cc: Conner, Dale P; Yu, Lawrence; Adams, Wallace P; Sanchez, Aida L; Dandamudi, Suman*; Gong, Li; Chun, Nam; Margand, Iain; Howard, Eda; Li, Bing

Subject: RE: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of First Generic Checklists

Please note that DBE has completed all four checklist reviews for Omega 3-Acid Ethyl Esters Capsule and loaded them in DFS. Please refer to the reviews at DFS for details.

Thanks,

Bing

From: Nguyen, Hoainhon T
Sent: Friday, January 23, 2009 10:56 AM
To: Shimer, Martin
Cc: Conner, Dale P; Yu, Lawrence; Adams, Wallace P; Li, Bing; Sanchez, Aida L; Dandamudi, Suman*; Gong, Li; Chun, Nam; Margand, Iain; Howard, Eda; Nguyen, Hoainhon T
Subject: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of First Generic Checklists

Good morning Marty,

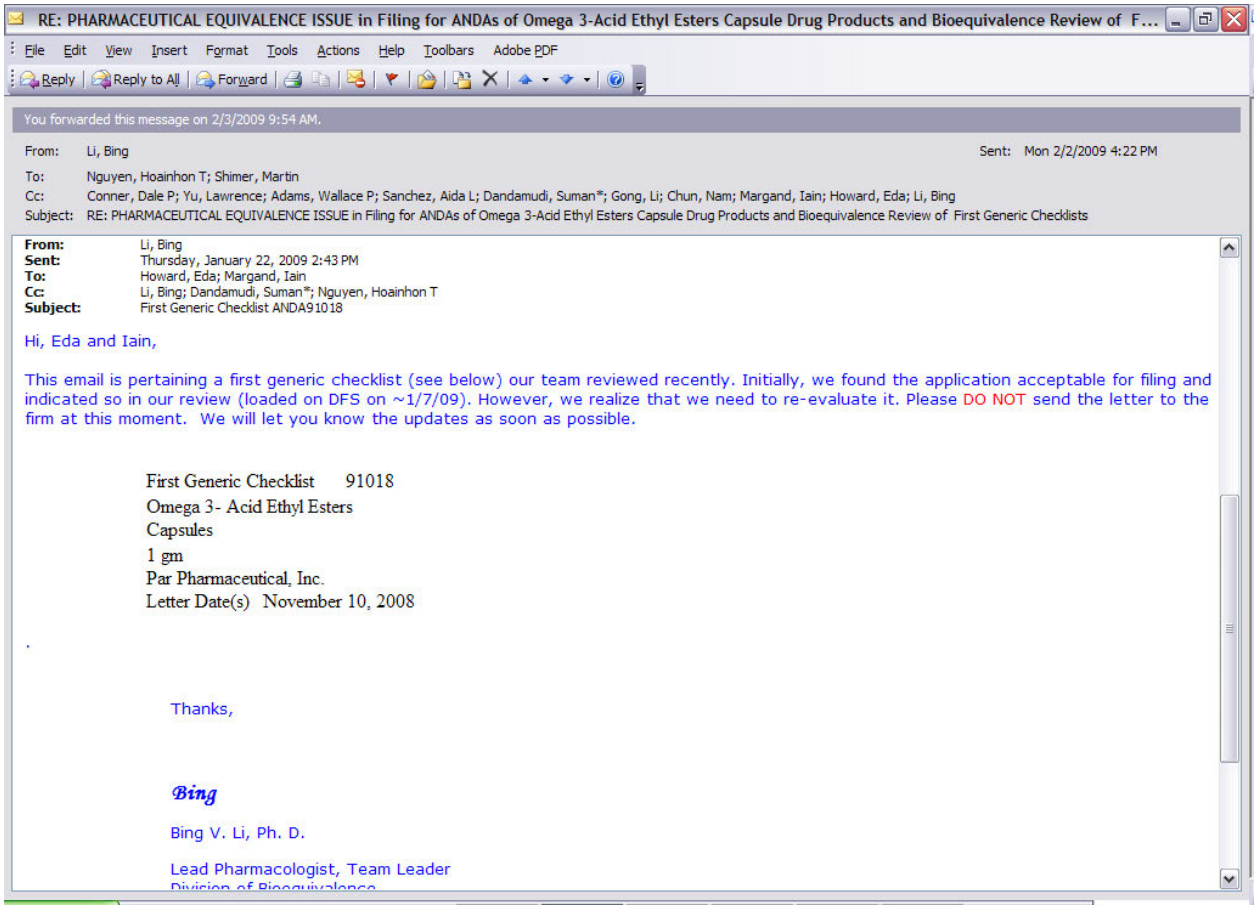
The DBE1 is currently requested by your division to review the Bioequivalence Checklists of the following ANDAs: 91018 (Par), 91028 (Teva), 90973 (Apotex), (b) (4)
(b) (4) of the above drug product. The Science Team has recently drafted a guidance for evaluating the generic versions of the drug product (attached). Per the draft guidance, in addition to the in vivo bioequivalence study and dissolution testing recommendations, there are recommendations related to the PHARMACEUTICAL EQUIVALENCE for the generic drug products. Per Wally and Lawrence of the Science Team, the issue of PHARMACEUTICAL EQUIVALENCE is complex and very important for this drug product, and should be addressed satisfactorily in each application ***before it is accepted for filing***.

Per Dale, the DBE1/Team 8 will review only the portion of the applications related to the in vivo bioequivalence and dissolution/rupture testing to make sure the in vivo and in vitro data are sufficiently presented for the purpose of demonstrating bioequivalence. Please consult the Science Team for the portion of the applications related to the PHARMACEUTICAL EQUIVALENCE of the drug products before accepting the ANDAs for filing.

Thanks,
Hoai

<< File: Omega-3-acid ethyl esters Draft Option Recommendations042108 (2).doc >>

From: Li, Bing
Sent: Thursday, January 22, 2009 2:43 PM
To: Howard, Eda; Margand, Iain
Cc: Li, Bing; Dandamudi, Suman*; Nguyen, Hoainhon T
Subject: First Generic Checklist ANDA91018



RE: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of F...

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You forwarded this message on 2/3/2009 9:54 AM.

From: Li, Bing Sent: Mon 2/2/2009 4:22 PM

To: Nguyen, Hoainhon T; Shimer, Martin

Cc: Conner, Dale P; Yu, Lawrence; Adams, Wallace P; Sanchez, Aida L; Dandamudi, Suman*; Gong, Li; Chun, Nam; Margand, Iain; Howard, Eda; Li, Bing

Subject: RE: PHARMACEUTICAL EQUIVALENCE ISSUE in Filing for ANDAs of Omega 3-Acid Ethyl Esters Capsule Drug Products and Bioequivalence Review of First Generic Checklists

From: Li, Bing
Sent: Thursday, January 22, 2009 2:43 PM
To: Howard, Eda; Margand, Iain
Cc: Li, Bing; Dandamudi, Suman*; Nguyen, Hoainhon T
Subject: First Generic Checklist ANDA91018

Hi, Eda and Iain,

This email is pertaining a first generic checklist (see below) our team reviewed recently. Initially, we found the application acceptable for filing and indicated so in our review (loaded on DFS on ~1/7/09). However, we realize that we need to re-evaluate it. Please DO NOT send the letter to the firm at this moment. We will let you know the updates as soon as possible.

First Generic Checklist 91018
Omega 3- Acid Ethyl Esters
Capsules
1 gm
Par Pharmaceutical, Inc.
Letter Date(s) November 10, 2008

.

Thanks,

Bing

Bing V. Li, Ph. D.

Lead Pharmacologist, Team Leader
Division of Bioequivalence

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: NOVEMBER 10, 2008	☒
1.2.1	**Form FDA 3674 (PDF) YES** Box "B" (see 1/12/09 amendment)	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒

1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) PIV '077 exp. 3/26/2013 '667 exp. 8/27/2018 2. Paragraph: (Check all certifications that apply) PIII '594 exp. 8/4/09 MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☐ 3. Expiration of Patent(s): 8-27-2018 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: M-64 exp. 6/12/2010 NCE exp. 11/10/09	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Y b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒
1.12.11	**Basis for Submission** NDA# : 21-654 Ref Listed Drug: LOVAZA Firm: SMITHKLINE BEECHAM ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Omega-3-acid ethyl esters 3. Inactive ingredients 4. Route of administration Oral 5. Dosage Form Gel capsules 6. Strength 1 g	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☐
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? No (If yes, send email to Labeling Reviewer indicating such.)	☒

1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** Y **Word Processed e.g., MS Word** Y A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** Y **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF Y** **Word Processed e.g., MS Word** Y **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Table 4. Bioanalytical Method Validation Table 6. Formulation Data **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Table 3. Statistical Summary of the Comparative BA Data **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) YES 2. Function or Responsibility YES 3. Type II DMF number for API DMF# (b) (4) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization** Refer to DMF# (b) (4)	☐
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2 Analytical Procedures** Y **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples see 3.2.S.4.4 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5 Justification of Specification** Y	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems** Refer to DMF# (b) (4)	☐
3.2.S.7	**Stability** Refer to DMF# (b) (4)	☐

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition Y 2. Inactive ingredients and amounts are appropriate per IIG Y –see below	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** Y **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) capsules 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement Y **3.2.P.3.4 Controls of Critical Steps and Intermediates** Y **3.2.P.3.5 Process Validation and/or Evaluation** N/A 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) see 3.2.P.4.4 **3.2.P.4.2 Analytical Procedures** Y **3.2.P.4.3 Validation of Analytical Procedures** N/A – USP/NF **3.2.P.4.4 Justification of Specifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** Y **3.2.P.5.2 Analytical Procedures** Y **3.2.P.5.3 Validation of Analytical Procedures** Y – see 3.2.R Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Y 2. Same lot numbers Y **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form lot# 216809 **3.2.P.5.5 Characterization of Impurities** Y **3.2.P.5.6 Justification of Specifications** Y	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data 3. Packaging Configuration and Sizes (b) (4) 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☐
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period (b) (4) months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data Y 2. Batch numbers on stability records the same as the test batch 216809	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) N/A** **3.2.R.2.S Comparability Protocols N/A** **3.2.R.3.S Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation see attached Theoretical Yield Actual Yield Packaged Yield **3.2.R.1.P.2 Information on Components** N/A **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

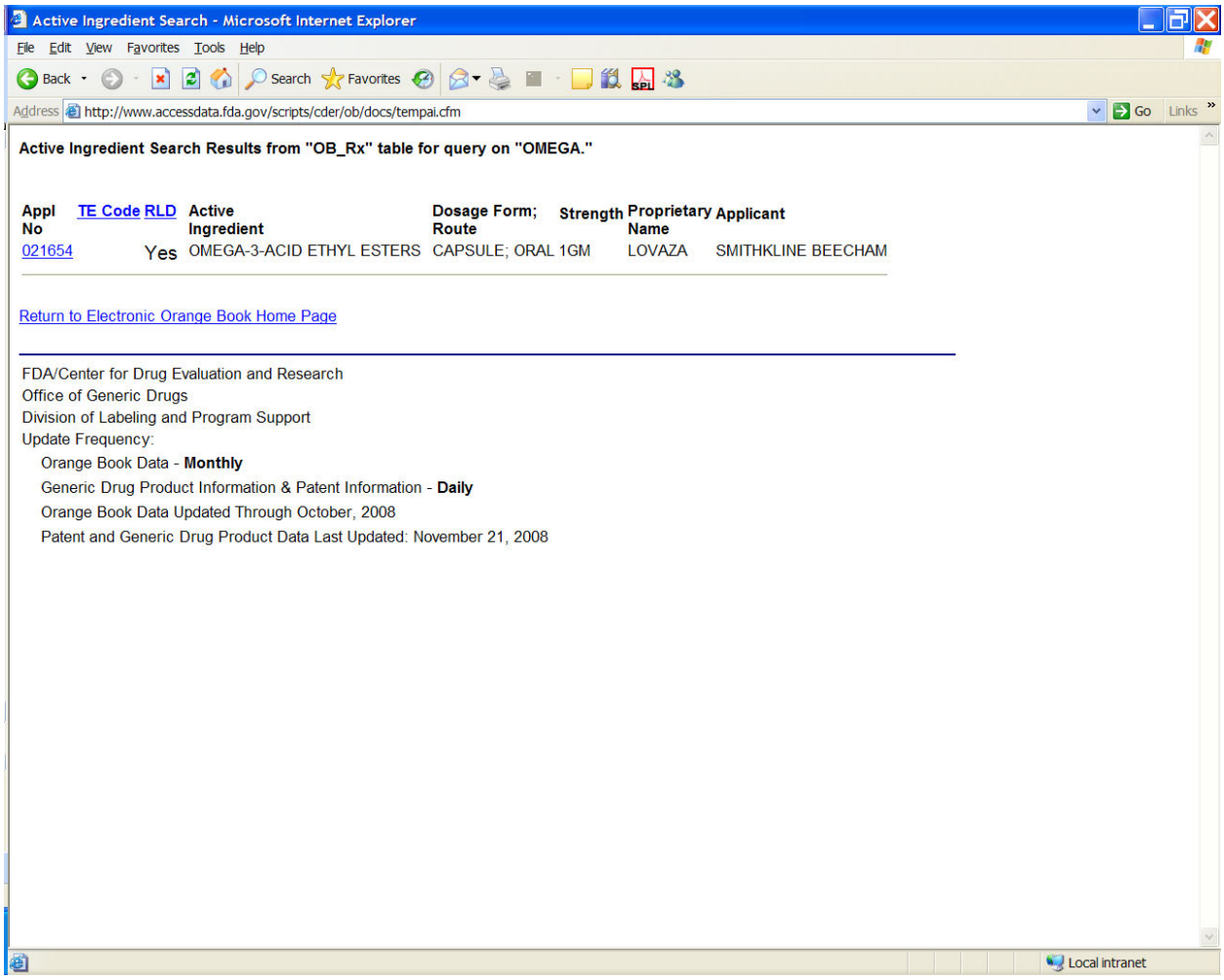
ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) N/A **2. Lot Numbers of Products used in BE Study(ies):** 21680902 **3. Study Type:** (Continue with the appropriate study type box below)	☒

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 10. Study Information Table 12. Dropout Information Table 13. Protocol Deviations **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information Table 16. Composition of Meal Used in Fed Bioequivalence Study **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **5.3.7** **Case Report Forms and Individual Patient Listing**	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008


Active Ingredient Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
Go Links
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Appl No
TE Code
RLD
Active Ingredient
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Strength
Proprietary Name
Applicant
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CAPSULE; ORAL
1GM
LOVAZA
SMITHKLINE BEECHAM
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FDA/Center for Drug Evaluation and Research
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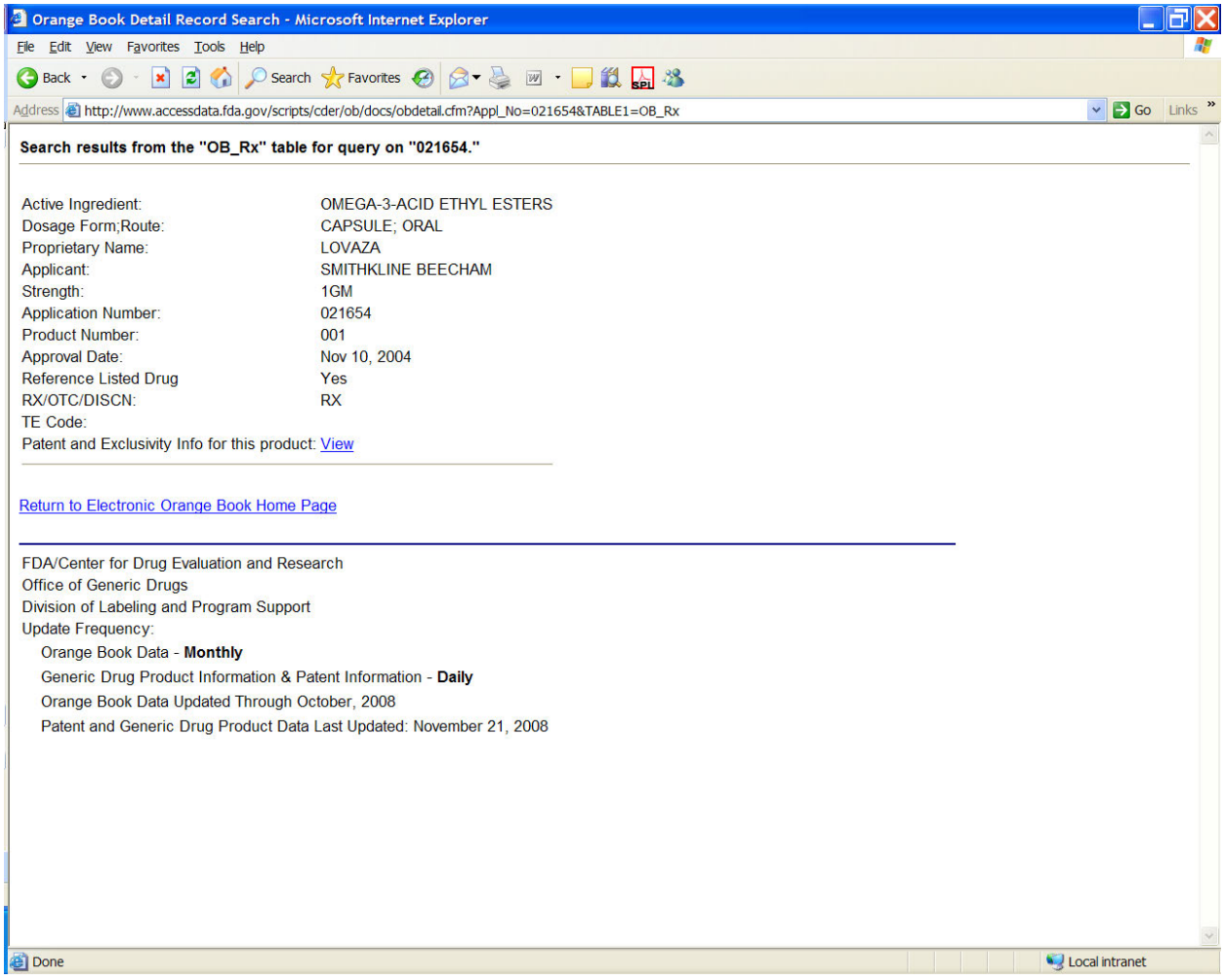
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through October, 2008
Patent and Generic Drug Product Data Last Updated: November 21, 2008
Local intranet


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021654&TABLE1=OB_Rx
Go Links
Search results from the "OB_Rx" table for query on "021654."
Active Ingredient: OMEGA-3-ACID ETHYL ESTERS
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: LOVAZA
Applicant: SMITHKLINE BEECHAM
Strength: 1GM
Application Number: 021654
Product Number: 001
Approval Date: Nov 10, 2004
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through October, 2008
Patent and Generic Drug Product Data Last Updated: November 21, 2008
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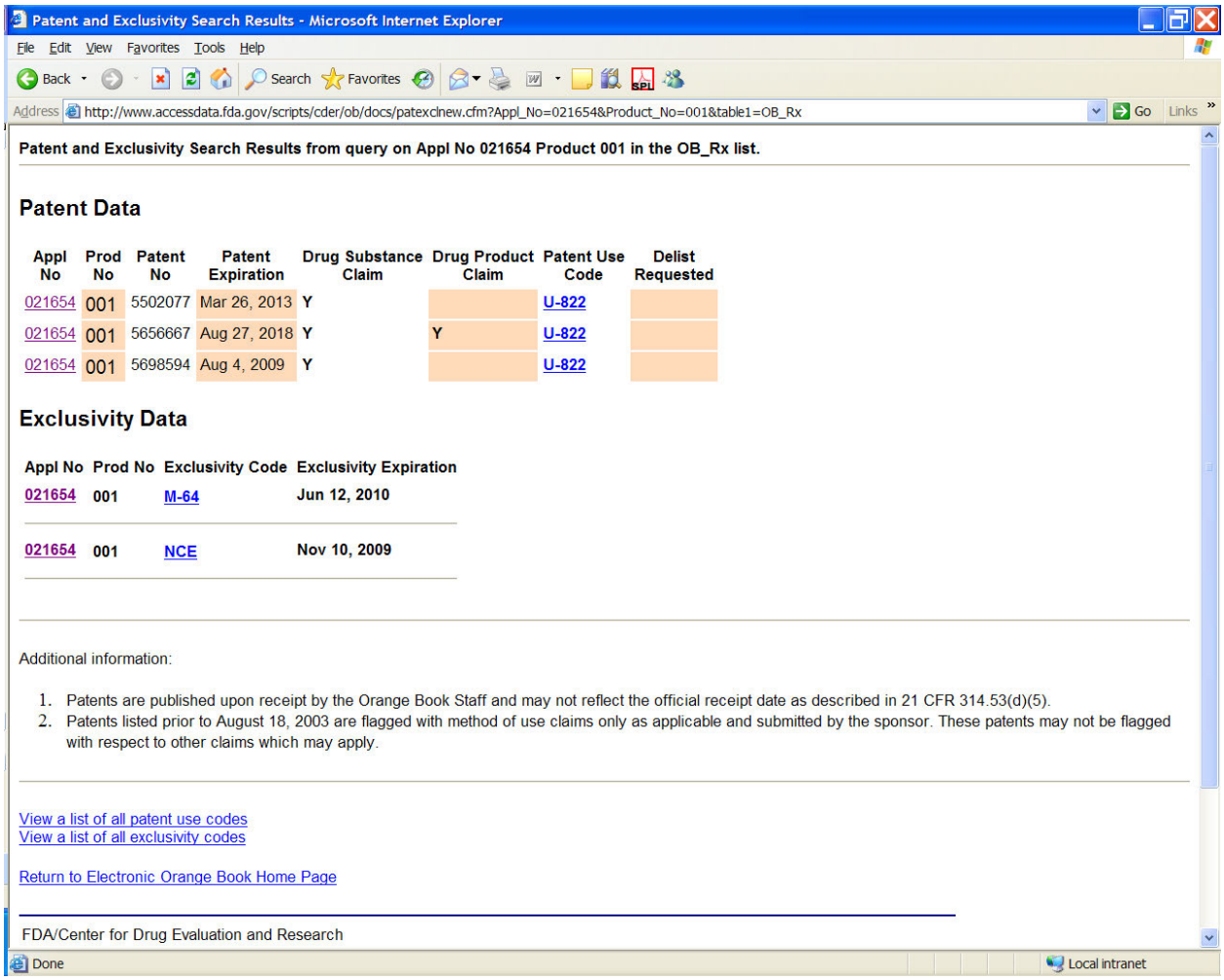

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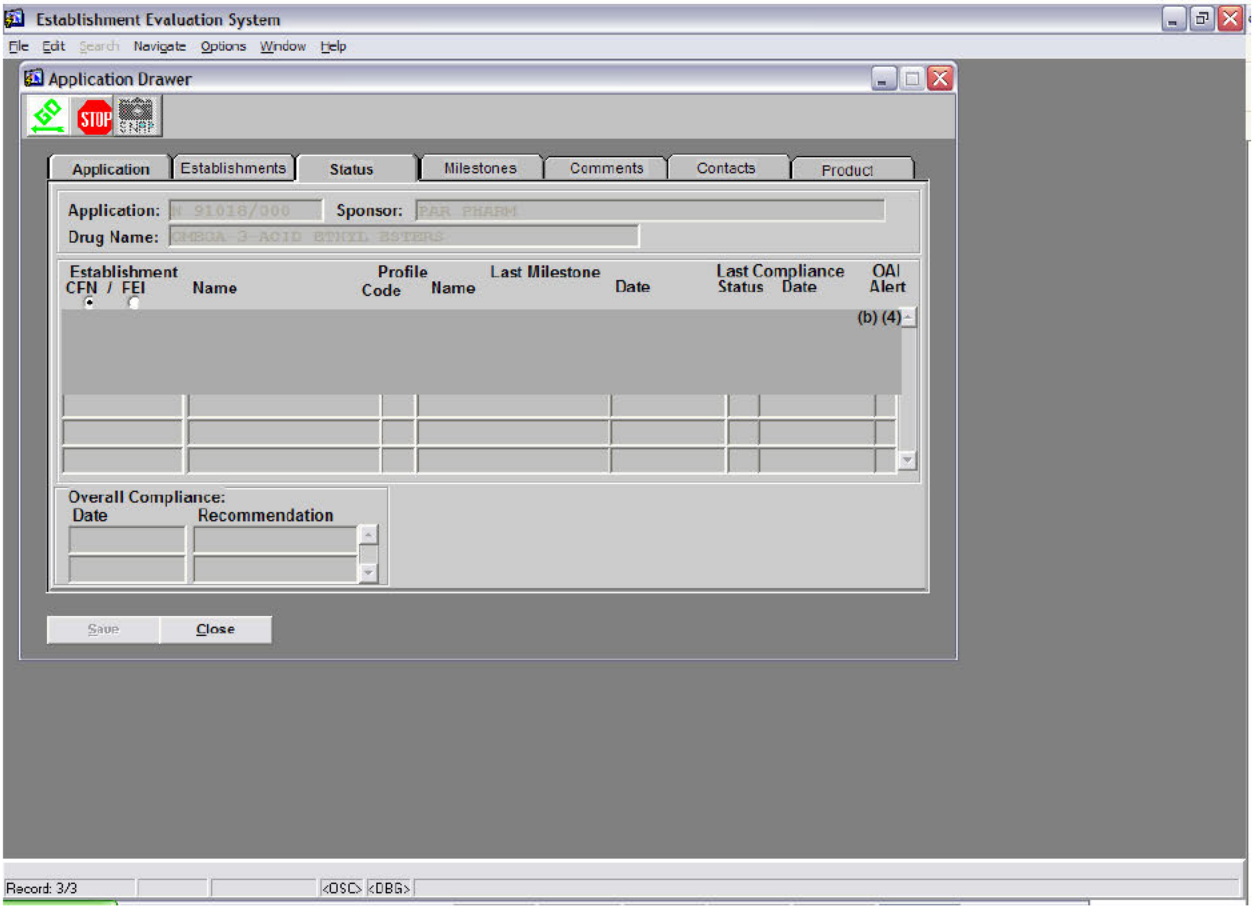
(b) (4)

Table 3.1 Statistical Summary of the Comparative Bioavailability Data

Lovaza Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Pharmacokinetic Study (Study No. 2008-1806)				
Eicosapentaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	45.03	29.97	150.27	48.32 - 467.28
Cmax	3.10	2.69	115.13	66.08 - 200.60
Docosahexaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	38.06	68.05	55.94	29.82 - 104.93
Cmax	5.30	7.22	73.48	57.97 - 93.14
Eicosapentaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	0.327	0.393	83.17	59.05 - 117.16
Cmax	0.074	0.063	116.35	90.24 – 150.02
Docosahexaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	2.045	2.786	73.41	53.60 - 100.54
Cmax	0.500	0.455	109.95	84.04 - 143.85

Lovaza Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Pharmacokinetic Study (Study No. 2008-1807)				
Eicosapentaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	802.36	746.43	107.49	92.83 - 124.47
Cmax	50.41	56.04	89.97	71.05 - 113.92
Docosahexaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	260.64	183.86	141.76	88.45 - 227.22
Cmax	27.54	29.47	93.43	59.98 - 145.55
Eicosapentaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	3.665	4.049	90.53	70.01 - 117.06
Cmax	0.495	0.669	73.98	50.50 - 108.38
Docosahexaenoic acid (free fatty acids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	7.859	8.631	91.05	61.33 - 135.16
Cmax	1.350	1.810	74.54	50.49 - 110.05

Omega-3-Acid Ethyl Esters Dose (4 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. 2008-1835)				
Eicosapentaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	1636.09	1500.30	109.05	102.53 - 115.99
Cmax	73.02	64.50	113.21	106.88 - 119.92
Docosahexaenoic acid (total lipids)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	760.24	684.71	111.03	103.20 - 119.45
Cmax	45.11	41.90	107.66	100.32 - 115.54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PAR PHARM
Drug Name:
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Establishment CFN / FEI
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BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 91018 **FIRM NAME** Par Pharmaceutical, Inc.

DRUG NAME Omega 3- Acid Ethyl Ester

DOSAGE FORM Capsules, 1 gm

SUBJ: Request for examination of: Bioequivalence study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Suman Dandamudi, Ph.D.
Reviewer

_____ Date: _____
Bing Li, Ph.D.
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Fasted Pharmacokinetic Study of Lovaza®: 2008-1806 (Pilot Study) Fed Pharmacokinetic Study of Lovaza®: 2008-1807 (Pilot Study) Fed BE study No: 2008-1835
Assay Methodology	☒	☐			
Procedure SOP	☒	☐			General SOPs and SOP for Reanalysis are provided
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			AUCT, and Cmax
Adverse Events	☒	☐			
IRB Approval	☒	☐			ERB Approval
Dissolution Data	☐	☒			Not applicable No Individual capsule rupture test data was submitted
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			Representative Chromatograms (20% serially selected)
Consent Forms	☒	☐			
Composition	☒	☐			Module 2
Summary of Study	☒	☐			
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted	☒	☐			SAS files are available in EDR

Protocol Deviations	☒	☐			
Clinical Site	☒	☐			Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6
Analytical Site	☒	☐			(b) (4)
Study Investigators	☒	☐			
Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☒	☐			
BIO Batch Size	☐	☒			
Assay of Active Content Drug	☐	☒			N/A
Content Uniformity	☐	☒			N/A
Date of Manufacture	☒	☐			Test- 17 July 2008
Exp. Date of RLD	☒	☐			April 2011
BioStudy Lot Numbers	☒	☐			Test- 21680902 Reference- 803040W
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☐	☒			N/A

Lovaza® is a lipid regulating agent. It is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglyceride levels. Each one gram capsule of Lovaza® (Omega 3-acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of Eicosapentaenoic acid (EPA- 465 mg) and docosahexaenoic acid (DHA- 375 mg).

Additional Comments Regarding the ANDA:

1. This submission is an electronic application. All of the requested information is located in the electronic document room (EDR).

2. The firm has conducted the pilot study on the RLD and submitted the results of Pharmacokinetic studies of Lovaza® 1000 mg capsules under fasting and fed conditions.

3. The RLD labeling of Lovaza® states the product to be taken along with the meals. So the firm has submitted only fed BE studies on the Omega 3-Acid Ethyl Ester Capsules, 1000 mg. The RLD product used by the firm for this application is Lovaza® (Omega 3-Acid Ethyl Ester) Capsules by Smith Kline Beecham (NDA #: 21-654).

4. The firm measured EPA and DHA levels from the free fatty acids of plasma and from the plasma total lipids. Since endogenous levels of EPA and DHA are present, so the firm measured the concentrations in 24 hours prior to dosing and were used to adjust for baseline post-dose levels time-point by time-point.

5. The Pharmacokinetic parameters were estimated based on baseline adjusted EPA and DHA levels from total lipids and from free fatty acids of plasma for each subject.

   EPA(total lipids), N= 70 (point estimate and 90% confidence intervals)
   are LAUCT = 109.05%, 102.53-115.99%, LCmax = 113.21%, 106.88-119.92%.

   DHA (total lipids), N= 70 (point estimate and 90% confidence intervals)
   are LAUCT = 111.03%, 103.20-119.45% and LCmax = 107.66%, 100.32-115.54%.

6. The firm stated that all capsules rupture within the 15 minute requirement. However they did not provide the data for individual dosage units.

7. The firm submitted all of the requested BIO summary tables except capsule rupture test results.

8. **There is currently no control document review or Bioequivalence Recommendation guidance for Omega 3-Acid Ethyl Ester Capsules. OGD Science Staff has drafted the bioequivalence recommendations for this product (shown below). However this is a "DRAFT ONLY" and not yet finalized.**

(b) (4)

[redacted]

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(b) (4)

[redacted]

Dissolution Test Method and Sampling Times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

(b) (4)

[redacted]

Additional Comments:

1. The draft guidance recommends for the BE studies, drug treatment be conducted for 7 days to reach the steady state i.e **multiple doses** should be administered. The appropriate parameters for BE statistics are increasing in maximum blood EPA and DHA concentration (Cmaxss) and increasing in area under the blood EPA and DHA concentration versus time curve (AUCss(0-tau)) from day prior to drug treatment to the day after reaching the steady state. These recommendations were made based on the NDA 21-654.

2. However the firm conducted a **Single dose** BE study on Omega 3-Acid Ethyl Ester Capsules (4 × 1000 mg) comparing to the RLD, Lovaza® (Omega 3-Acid Ethyl Ester) capsules (4 × 1000 mg). Their analytical method is shown to be sensitive to measure the concentrations of EPA and DHA from plasma total lipids. The Plasma concentration time profile was developed and the pharmacokinetic parameters were estimated based on the single dose. The 90% confidence intervals for AUCt and Cmax for EPA and DHA were shown to be within the acceptance limit of [80;125] with baseline correction. Therefore, the firm has submitted adequate data and information purported to demonstrate bioequivalence between the test and RLD products. For this reason, the DBE accepts the firm's submission of the pilot and pivotal bioequivalence studies FOR FILING.

3. Based on OCPB review of NDA # 21-654, the dissolution test is not adequately justified for this product, since the drug substance is oil which is insoluble in water. A rupture test is more appropriate for quality control purpose.

4. Based on this rationale, DBE recommends that the Rupture Test should be conducted on this product, and accepts the firm's rupture test results for the test product.

Note to Reviewer:

- The firm did not submit the Bio Batch Size and the Long Term Storage Stability data.
- The firm should provide individual Rupture Test data for 12 capsules each of test and reference products.

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/s/

Martin Shimer

3/9/2009 10:49:29 AM

ADDENDUM TO
BIOEQUIVALENCE CHECKLIST FOR FIRST GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# 91-018 **FIRM NAME** Par Pharmaceutical, Inc.

DRUG NAME Omega 3- Acid Ethyl Ester

DOSAGE FORM Capsules, 1 gm

SUBJ: Request for examination of: Bioequivalence study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Suman Dandamudi, Ph.D.
Reviewer

_____ Date: _____
Bing Li, Ph.D.
Team Leader

Please see the original DBE Checklist review in DFS (N 091018 N 000 10-Nov-2008).

This addendum is to revise the DBE's previous review for a First Generic ANDA Checklist of the above submission. The application was found acceptable for filing by DBE, with respect to in vivo and in vitro bioequivalence testing, on 1/07/09 (N 091018 N 000 10-Nov-2008). This addendum contains a correction for the Comment #3 in the original review. This addendum also adds DBE's recommendation to the OGD Regulatory Support Staff concerning the PHARMACEUTICAL EQUIVALENCE review of the ANDA BEFORE filing.

Under "Additional Comments Regarding the ANDA: Comment #3", page 4 of the original review, it was stated that:

"*The RLD labeling of Lovaza® states the product to be taken along with the meals. So the firm has submitted only fed BE studies on the Omega 3-Acid Ethyl Ester Capsules, 1000 mg.*"

The above statements should be corrected to the following statements:

"*The RLD labeling of Lovaza® states that "Patients should be placed on an appropriate lipid-lowering diet before receiving LOVAZA, and should continue this diet during treatment with LOVAZA. In clinical studies, LOVAZA was administered with meals.""*

Although the RLD labeling does not specify the drug product to be taken with meals, the DBE considers that a fed BE study is acceptable for this drug product for the following reasons:

- In this application, Par Pharmaceuticals conducted two pilot pharmacokinetic studies on the RLD under both fasting and fed conditions, and the results are as following:

EPA (Total lipids)

Parameter	**Geometric mean ± %CV**			
	Test		**Reference**	
	Fasting	**Fed**	**Fasting**	**Fed**
AUC0-t (µg·hr/mL)	45.03 ± 35	802.36 ± 25	29.97 ± 66	746.43 ± 32
Cmax (µg/mL)	3.10 ± 27	50.41 ± 29	2.69 ± 55	56.04 ± 34

DHA (Total lipids)

Parameter	**Geometric mean ± %CV**			
	Test		**Reference**	
	Fasting	**Fed**	**Fasting**	**Fed**
AUC0-t (µg·hr/mL)	38.06 ± 99	260.64 ± 42	68.05 ± 50	183.86 ± 52
Cmax (µg/mL)	5.30 ± 39	27.54 ± 40	7.22 ± 37	29.47 ± 55

From the above results, very low level of EPA and DHA were observed in the fasting study, as compare to the fed study, which could render the fasting study results unreliable. The firm therefore performed the pivotal study under fed condition only.

- Similar results were observed in another application for Omega 3-Acid Ethyl Ester Capsules from Teva Pharms (ANDA 91-028). The overall absorption of the EPA and DHA appeared to be limited under fasting condition and thus the firm performed the pivotal study under fed condition.

- It is also noticed that the clinical studies for Lovaza® (Omega 3-Acid Ethyl Ester) Capsules by Smith Kline Beecham (NDA #: 21-654) were conducted only under fed condition.

- Based on the above reasons, the DBE has recommended accepting for filing the fed BE study conducted for demonstration of bioequivalence.

Therefore, the application remains acceptable FOR FILING from the DBE's point of view with respect to in vivo and in vitro bioequivalence testing.

In addition, the DBE has the following note to the Regulatory Support Division:

Note to the Regulatory Support Division:

Please note that the DBE1/Team 8 has reviewed only the portion of the application related to the in vivo bioequivalence and dissolution/rupture testing to make sure the in vivo and in vitro data are sufficiently presented for the purpose of demonstrating bioequivalence. Please consult the Science Team for the portion of the application related to the PHARMACEUTICAL EQUIVALENCE of the drug products before accepting the ANDA for filing.

ANDA# 91-018

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7383	11/10/2008	Other	Addendum	0	0
				Bean Total:	0

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/s/

Bing Li

1/28/2009 02:18:55 PM

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 91018 **FIRM NAME** Par Pharmaceutical, Inc.

DRUG NAME Omega 3- Acid Ethyl Ester

DOSAGE FORM Capsules, 1 gm

SUBJ: Request for examination of: Bioequivalence study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Suman Dandamudi, Ph.D.
Reviewer

_____ Date: _____
Bing Li, Ph.D.
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Fasted Pharmacokinetic Study of Lovaza®: 2008-1806 (Pilot Study) Fed Pharmacokinetic Study of Lovaza®: 2008-1807 (Pilot Study) Fed BE study No: 2008-1835
Assay Methodology	☒	☐			
Procedure SOP	☒	☐			General SOPs and SOP for Reanalysis are provided
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			AUCT, and Cmax
Adverse Events	☒	☐			
IRB Approval	☒	☐			ERB Approval
Dissolution Data	☐	☒			Not applicable No Individual capsule rupture test data was submitted
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			Representative Chromatograms (20% serially selected)
Consent Forms	☒	☐			
Composition	☒	☐			Module 2
Summary of Study	☒	☐			
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted)	☒	☐			SAS files are available in EDR
Randomization Schedule	☒	☐			

Protocol Deviations	☒	☐			
Clinical Site	☒	☐			Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada M1S 3V6
Analytical Site	☒	☐			(b) (4)
Study Investigators	☒	☐			
Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☒	☐			
BIO Batch Size	☐	☒			
Assay of Active Content Drug	☐	☒			N/A
Content Uniformity	☐	☒			N/A
Date of Manufacture	☒	☐			Test- 17 July 2008
Exp. Date of RLD	☒	☐			April 2011
BioStudy Lot Numbers	☒	☐			Test- 21680902 Reference- 803040W
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☐	☒			N/A

Lovaza® is a lipid regulating agent. It is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglyceride levels. Each one gram capsule of Lovaza® (Omega 3-acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of Eicosapentaenoic acid (EPA- 465 mg) and docosahexaenoic acid (DHA- 375 mg).

Additional Comments Regarding the ANDA:

1. This submission is an electronic application. All of the requested information is located in the electronic document room (EDR).

2. The firm has conducted the pilot study on the RLD and submitted the results of Pharmacokinetic studies of Lovaza® 1000 mg capsules under fasting and fed conditions.

3. The RLD labeling of Lovaza® states the product to be taken along with the meals. So the firm has submitted only fed BE studies on the Omega 3-Acid Ethyl Ester Capsules, 1000 mg. The RLD product used by the firm for this application is Lovaza® (Omega 3-Acid Ethyl Ester) Capsules by Smith Kline Beecham (NDA #: 21-654).

4. The firm measured EPA and DHA levels from the free fatty acids of plasma and from the plasma total lipids. Since endogenous levels of EPA and DHA are present, so the firm measured the concentrations in 24 hours prior to dosing and were used to adjust for baseline post-dose levels time-point by time-point.

5. The Pharmacokinetic parameters were estimated based on baseline adjusted EPA and DHA levels from total lipids and from free fatty acids of plasma for each subject.

   EPA(total lipids), N= 70 (point estimate and 90% confidence intervals)
   are LAUCT = 109.05%, 102.53-115.99%, LCmax = 113.21%, 106.88-119.92%.

   DHA (total lipids), N= 70 (point estimate and 90% confidence intervals)
   are LAUCT = 111.03%, 103.20-119.45% and LCmax = 107.66%, 100.32-115.54%.

6. The firm stated that all capsules rupture within the 15 minute requirement. However they did not provide the data for individual dosage units.

7. The firm submitted all of the requested BIO summary tables except capsule rupture test results.

8. There is currently no control document review or Bioequivalence Recommendation guidance for Omega 3-Acid Ethyl Ester Capsules. OGD Science Staff has drafted the bioequivalence recommendations for this product (shown below). However this is a "DRAFT ONLY" and not yet finalized.

(b) (4)

[redacted]

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(b) (4)

Dissolution Test Method and Sampling Times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

(b) (4)

Additional Comments:

1. The draft guidance recommends for the BE studies, drug treatment be conducted for 7 days to reach the steady state i.e **multiple doses** should be administered. The appropriate parameters for BE statistics are increasing in maximum blood EPA and DHA concentration (Cmaxss) and increasing in area under the blood EPA and DHA concentration versus time curve (AUCss(0-tau)) from day prior to drug treatment to the day after reaching the steady state. These recommendations were made based on the NDA 21-654.

2. However the firm conducted a **Single dose** BE study on Omega 3-Acid Ethyl Ester Capsules (4 × 1000 mg) comparing to the RLD, Lovaza® (Omega 3-Acid Ethyl Ester) capsules (4 × 1000 mg). Their analytical method is shown to be sensitive to measure the concentrations of EPA and DHA from plasma total lipids. The Plasma concentration time profile was developed and the pharmacokinetic parameters were estimated based on the single dose. The 90% confidence intervals for AUCt and Cmax for EPA and DHA were shown to be within the acceptance limit of [80;125] with baseline correction. Therefore, the firm has submitted adequate data and

information purported to demonstrate bioequivalence between the test and RLD products. For this reason, the DBE accepts the firm's submission of the pilot and pivotal bioequivalence studies FOR FILING.

3. Based on OCPB review of NDA # 21-654, the dissolution test is not adequately justified for this product, since the drug substance is oil which is insoluble in water. A rupture test is more appropriate for quality control purpose.

4. Based on this rationale, DBE recommends that the Rupture Test should be conducted on this product, and accepts the firm's rupture test results for the test product.

Note to Reviewer:

- The firm did not submit the Bio Batch Size and the Long Term Storage Stability data.
- The firm should provide individual Rupture Test data for 12 capsules each of test and reference products.

ANDA# 91-018

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7084	11/10/2008	Paragraph 4	Paragraph 4 Checklist	1	1
				Bean Total:	1

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/s/

Bing Li

1/7/2009 02:34:46 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : November 21, 2008

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 91-018 for Omega 3- Acid Ethyl Esters Capsules, 1 gram to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Par Pharmaceutical Inc. has submitted ANDA 91-018 for Omega 3- Acid Ethyl Esters Capsules, 1 gram. The ANDA contains a certification pursuant to 21 USC 355(j) (5) (B) (IV) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Par Pharmaceutical Inc. on November 10, 2008 for its Omega 3- Acid Ethyl Esters product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms to an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

Eda Howard
12/2/2008 02:42:27 PM
APPLICATIONS EXA