CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205060Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

Date: April 24, 2014

From: Martin Haber, Ph.D., Review Chemist

Subject: EES for NDA 205060 Epanova Capsules

On April 24, 2014 the Office of Compliance issued an "Acceptable" overall recommendation for this NDA into the EES system. There are no pending cGMP inspection issues, see attached report.

The chemistry recommendation is Approval as per Chemistry Review #1, dated 3/26/2014. There are no pending CMC issues.

R/D Init by: Dr. D. Christodoulou, Branch Chief, DNDQAIII, BVII

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205060/000	**Sponsor:**	ASTRAZENECA PHARMS
Org. Code:	510		1800 CONCORD PIKE
Priority:	5		WILMINGTON, DE 198038355
Stamp Date:	05-JUL-2013	**Brand Name:**	EPANOVA (OMEFAS) CAPSULES
PDUFA Date:	05-MAY-2014	**Estab. Name:**	OMEGA 3- CARBOXYLIC ACIDS
Action Goal:		**Generic Name:**	
District Goal:	06-MAR-2014	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; CAPSULE; OMEGA-3-ACID [redacted] (b) (4)	1GM

FDA Contacts:	M. HABER	Prod Qual Reviewer		3017961675
	P. KUMAR	Product Quality PM	(HFD-800)	2404023722
	K. JOHNSON	Regulatory Project Mgr	(HFD-510)	3017961234

Overall Recommendation:	ACCEPTABLE	on 24-APR-2014	by R. XU	()	3017966187
	PENDING	on 09-APR-2014	by EES_PROD		
	PENDING	on 24-SEP-2013	by EES_PROD		
	PENDING	on 24-SEP-2013	by EES_PROD		
	PENDING	on 27-AUG-2013	by EES_PROD		
	PENDING	on 07-AUG-2013	by EES_PROD		
	PENDING	on 07-AUG-2013	by EES_PROD		
	PENDING	on 15-JUL-2013	by EES_PROD		
	PENDING	on 15-JUL-2013	by EES_PROD		

Establishment:	**CFN:** [redacted] (b) (4)	**FEI:** [redacted] (b) (4)	
	[redacted] (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-AUG-2013		
Decision:	ACCEPTABLE		

Reference ID: 3495425

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** **FEI:** 3004063541

BIOVECTRA, INC.
11 AVIATION ST

CHARLOTTETOWN, , CANADA

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-DEC-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9615009 **FEI:** 3003831171

CATALENT GERMANY SCHOMDORF GMBH
STEINBEISSTR. 2

SCHORNDORF, BADEN-W¿RTTEMBERG, GERMANY

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9610144 **FEI:** 3002808098

CATALENT PHARMA EBERBACH GMBH
GAMMELSBACHER STRABE 2

EBERBACH, BADEN-W¿RTTEMBERG, GERMANY

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: CAPSULES, SOFT GELATIN **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-DEC-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Reference ID: 3495425

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-APR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

INTERMEDIATE OTHER TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-APR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-AUG-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Reference ID: 3495425

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-AUG-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-AUG-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Reference ID: 3495425

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

/s/

MARTIN T HABER
04/24/2014

DANAE D CHRISTODOULOU
04/24/2014

NDA 205-060

Epanova™ (Omega-3-Carboxylic Acids) Capsules 1 g

Omthera Pharmaceuticals, Inc.

Martin Haber, PhD
Xavier Ysern, PhD

ONDQA/ DNQA III/ Branch VII

CMC Review for DMEP

Reference ID: 3478314

Table of Contents

Reference ID: 3478314

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA: (b) (4)

2. Review #: 1

3. Review Date: 26-Mar-2014

4. Reviewer(s): Martin Haber, PhD, and Xavier Ysern, PhD

5. Previous Documents:

Previous Documents	Document Date
--	--

6. Submission(s) Being Reviewed:

Submission(s) Reviewed	Document Date
Original	05-Jul-2013
Amendment	02-Aug-2013 (Quality/Stability Information)

7. Name and Address of Applicant:

Name:	Omthera Pharmaceutical, Inc.
Address:	707 State Road Princeton, NJ 08540
Representative:	Samia Siddiqui, PhD
Telephone:	(908) 741-6418

8. Drug Product Name/Code/Type:

a) Proprietary Name: Epanova™ (a lipid-altering agent, is a coated soft gelatin capsule contining a complex mixture of polyunsaturated free fatty acids derived from fish oils and includes multiple long-chain omega-3 and omega-6 fatty acids)
b) Non-Proprietary Name (USAN): Omega-3-Carboxylic Acids
c) Code Name/# (ONDC only): --
d) Chem. Type/Submission Priority: Chem. Type: 5 (New formulation or new manufacturer)
Submission Priority: S

9. Legal Basis For Submission: 505(b)(1)

10. Pharmacological Category: Lipid Altering Agent [Reduction of triglyceride, (b) (4) levels in adults with severe (500 mg/dL) hypertriglyceridemia.]

11. Dosage Form: [Soft Gel] Capsules

12. Strength/Potency: 1000 mg (1 g)

13. Route of Administration: Oral

14. Rx/OTC Dispensed: Rx

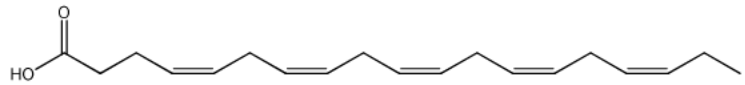
15. SPOTS (Special Products On-Line Tracking System): SPOTS product (form completed)

Reference ID: 3478314

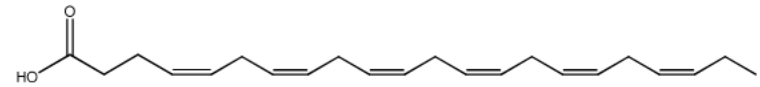
16. Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

The drug substance is a complex consisting of a mixture of polyunsaturated free fatty acids (PUFAs) derived from fish oils and includes multiple long-chain omega-3 and omega-6 fatty acids, with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) being the most abundant forms of omega-3 fatty acids, and (b) (4) the most abundant forms of omega-6 fatty acids.

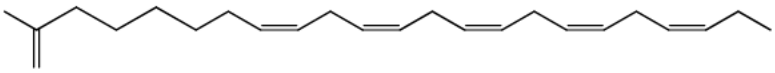
(EPS) Eicosapentaenoic acid (EPA)
$C_{20}H_{30}O_2$
MW: 302.451 g/mol
(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoic acid



(DHA) Docosahexaenoic acid
$C_{22}H_{32}O_2$
MW: 328.488 g/mol
(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid



(DPA) Docosapentaenoic acid
$C_{22}H_{34}O_2$
MW: 330.504 g/mol
(7Z,10Z,13Z,16Z,19Z)-docosa-7,10,13,16,19-pentaenoic acid



(b) (4)

17. Related/Supporting Documents:

A. DMFs:

DMF #	Holder	Item Referenced	Code[a]	Status[b]	Date Review Completed	LOA Date
Type II --	--	--				
Type III (b) (4)	(b) (4)		4 4	Adequate Adequate		13-Mar-2013 15-Mar-2013
Type IV (b) (4)			4	Adequate		15-Apr-2013

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

B. Other Documents:

Document	Application Number	Description
IND	107,616	Epanova (omefas) Capsules [Omthera Pharmaceuticals, Inc.]

Reference ID: 3478314

18. Status:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
EES	Pending		
Pharm/Tox	(b) (4) specification acceptable	26-Mar-2014	Karen Davis Bruno, PhD
Biopharm	Acceptable	24-Mar-2014	Houda Mahayni, PhD
Methods Validation	Revalidation of the methods by Agency laboratories is not recommended		Part of this review
OPDRA	Pending (multidisciplinary review)		
EA	Categorical exclusion granted		Part of this review
Microbiology	Adequate	19-Aug-2013	Bryant Riley, PhD

Reference ID: 3478314

Executive Summary Section

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval, pending satisfactory evaluation of the cGMP status of the manufacturing facilities by the Office of Compliance.

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

None.

II. Summary of Chemistry Assessments

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

- Drug Substance

The drug substance is a complex mixture of polyunsaturated fatty acids (PUFAs), predominately the omega-3 acids EPA (eicosapentaenoic acid, 55 %), DHA (docosahexaenoic acid, 20 %) and DPA (docosapentaenoic acid, (b) (4) %). It consistently contains (b) (4) omega-3 and (b) (4) omega-6 PUFA components. Total omega-3 fatty acids are limited to NLT (b) (4) % and total omega-6 fatty acids are limited to NMT (b) (4) %. (b) (4) the drug substance contains (b) (4).

The drug substance is purified from crude fish oil obtained from (b) (4). (b) (4) at sites in Nova Scotia and Prince Edward Island, Canada. (b) (4)

Drug substance specifications include tests for acid value saponification value, ester value, peroxide value, p-anisidine value, total oxidation value, cholesterol, oligomers, (b) (4), fatty acid composition (PUFAs, EPA, DHA, DPA, total omega-3 fatty acids, total omega-6 fatty acids, other polyunsaturated fatty acids, (b) (4)

The drug substance is stored (b) (4) and is stable for up to (b) (4) months. The requested (b) (4) month retest period is fully supported by the stability data.

- Drug Product

The drug product, Epanova Capsules, is a soft gelatin oblong capsule containing 1,000 mg (1 g) of the Omega-3-Carboxilic Acids drug substance, (b) (4), and coated with a red/brown pigmented polymeric coat. The components of capsule gel are Gelatin (capsule shell), Sorbitol ((b) (4)), Glycerol ((b) (4)) and purified water (b) (4). The capsule coating contains Ethyl acrylate and methyl methacrylate copolymer (b) (4)), Talc ((b) (4)), Titanium dioxide ((b) (4)), Iron oxide red ((b) (4)), Polysorbate 80 ((b) (4)), (b) (4) ((b) (4)). Coated capsules are printed with (b) (4) (printing ink). Capsule gel, capsule coating and printing ink components meet compendial requirements.

Drug product specifications include identity tests (appearance by visual inspection and identification by GC), purity tests (acid value, peroxide value, p-anisidine value, total oxidation value and Absorbance), strength tests (polyunsaturated free fatty acids content, EPA content, DHA content, EPA plus DHA content, and total omega-

Reference ID: 3478314

3 content), quality tests (uniformity of mass of single dose, average mass of contents, average mass of capsules, oligomers content, total glycerides content, α-tocopherol content, and quantitative capsule rupture test as in vitro dissolution release surrogate), and microbial tests.

The manufacturing method for Epanova gelatin capsules is a conventional process. (b) (4)

A risk analysis was used to establish which variables in the unit operations ((b) (4)) have the greatest impact on product quality. Their impact was judged by their effect in the critical quality attributes identified in the quality attributes, which allowed to developed and implemented appropriate controls thereby mitigating the risk to quality.

The drug product is supplied for commercialization in bottles of 60 capsules. The soft gelatin capsules are packaged in white, opaque high density polyethylene (HDPE) bottles. The closures are (b) (4) screw caps (b) (4). In addition, the capsules may be blister packaged in units of aluminum/aluminum foil for physician samples (3x2 blister pack). The individual blister sheet may be packaged as an individual blister card.

The stability data for the bulk packs of uncoated and coated capsules show a similar chemical stability to that observed for the capsules in the commercial and physician samples packs. The main change chemical change observed in the stability studies is (b) (4) . This reaction has been well characterized by the Applicant, and a statistical evaluation show that the (b) (4) will comply with the shelf-life acceptance criteria of (b) (4)% for at least 30 months when stored at 25 °C/60 % RH.

(b) (4), the Applicant points out, that (b) (4) are the main natural form of fats in human diet and fish oil (b) (4) that are marketed as dietary supplements. In vivo, triglycerides and diglycerides are converted into free fatty acids and mono-glycerides by digestive enzymes (i.e. pancreatic lipase), then packed into chylomicrons and taken up by the intestinal endothelium. The concept of using free fatty acids as the active ingredient in Epanova is to bypass the enzymatic process and thereby improve the relative bioavailability compared to products that contain the triglyceride or ethyl ester form of the fatty acids.

The available data for the commercial package (36-, 24-, 18-months) and physicians sample package (24-, 3-months) fully support the requested shelf-life of 30 months when stored at controlled room temperature condition of 25 °C (77 °F); excursions within the range of 15° to 30°C (59° to 86°F) are permitted as per USP controlled room temperature criteria.

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

As indicated in the labeling, Epanova® (omega-3-carboxylic acids) capsules are indicated as an adjunct to diet to reduce triglyceride (TG), (b) (4) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

(b) (4) The daily dosage should be taken as a single 2-gram dose (2 capsules). (b) (4) the daily dosage may be (b) (4) 4 grams per day, taken as a single 4-gram dose (4 capsules). Patients should be advised to swallow Epanova capsules whole. The capsules should not be broken open, crushed, dissolved or chewed.

Reference ID: 3478314

C. Basis for Approvability or Not-Approval Recommendation

The Application is recommended for Approval based on the review of the provided information on the drug substance (omega-3-carboxylic acids) and drug product (Epanova Capsules 1 g).

III. Administrative

A.	**Reviewer's Signature**	Martin Haber, PhD Xavier Ysern, PhD	Chemist/ CDER/ ONDQA/ DNDQA III/ Branch VII Chemist/ CDER/ ONDQA/ DNDQA III/ Branch VII
B.	**Endorsement Block**	Danae Christodoulou, PhD	Acting Branch Chief/ ONDQA/ DNDQA III/ Branch VII
C.	**CC Block**	Kati Johnson	Project Manager/ CDER/ OND/ ODE II/ DMEP

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Reference ID: 3478314

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

/s/

XAVIER J YSERN
03/27/2014

MARTIN T HABER
03/27/2014

DANAE D CHRISTODOULOU
03/27/2014
I concur with the reviewers' conclusion and recommendation

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marketing Applications

1. NEW DRUG APPLICATION NUMBER: 205060
2. DATES AND GOALS:

Letter Date: 7/3/2013	Submission Received Date : 7/5/2013
PDUFA Goal Date: 5/5/2014 (NDA is not part of "The Program")	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	(proposed) Epanova Capsules
Established or Non-Proprietary Name (USAN):	Omefas (not yet approved by USAN)
Dosage Form:	Soft capsules
Route of Administration	oral
Strength/Potency	1 g
Rx/OTC Dispensed:	Rx

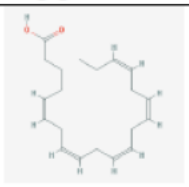
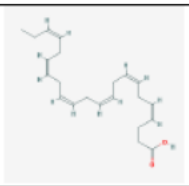
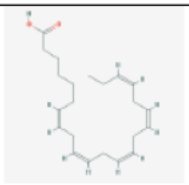
4. INDICATION: Reduction of triglyceride, [redacted] (b) (4) levels in adults with severe hypertriglyceridemia.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

In *section 3.2.S.1.1* "Nomenclature" it is explained that the name omefas is the proposed international non-proprietary name (INN) of this drug substance and that this name has been requested with the United States Adopted Names Council. The chemical (IUPAC nomenclature and Chemical Abstracts Service Registry Numbers (CAS) for each of the three most abundant forms of omega-3 fatty acids in the drug substance are also provided as follows:

- EPA: (*5Z, 8Z, 11Z, 14Z, 17Z*)-eicosa-5,8,11,14,17-pentaenoic acid;
- CAS 10417-94-4
- DHA: (*4Z, 7Z, 10Z, 13Z, 16Z, 19Z*)-docosa-4,7,10,13,16,19-hexaenoic acid;
- CAS 6217-54-5
- DPA: (*7Z, 10Z, 13Z, 16Z, 19Z*)-docosa-7,10,13,16,19-pentaenoic acid;
- CAS 24880-45-3

Reference ID: 3360198

Table 2.3.S-1. Structure Summaries for the Three Most Abundant Omega-3 Fatty Acids Contained in Omefas		
	Attribute	
EPA	Molecular Formula	$C_{20}H_{30}O_2$
	Molecular Weight	302.451 g/mol
	Amount contained in omefas	500 to 600 mg/g
	Structure	
DHA	Molecular Formula	$C_{22}H_{32}O_2$
	Molecular Weight	328.488 g/mol
	Amount contained in omefas	150 to 250 mg/g
	Structure	
DPA	Molecular Formula	$C_{22}H_{34}O_2$
	Molecular Weight	330.504 g/mol
	Amount contained in omefas	(b) (4) mg/g
	Structure	

6. NAME OF APPLICANT (as indicated on Form 356h): Omthera Pharmaceuticals

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code):	2
(Application Type):	505(b)(1)
Breakthrough Therapy	No
Responsible Organization:	Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Establishment Evaluation Request (EER)	x		Sent by the ONDQA PM on 15-JUL-2013.
Pharmacology/Toxicology	x		Review of limits on impurities and degradants.
Methods Validation			To be determined by Primary Reviewer
Environmental Assessment			To be determined by Primary Reviewer
CDRH		x	
Other			

FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
2	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
3	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		• Provide a copy of your application for a U.S. Adopted Name for your drug substance (reference is made to the U.S. Pharmacopeia Dictionary for details) and advise us of the progress of your application.

Reference ID: 3360198

Critical CMC Issues Previously Discussed with the Applicant (if any):

CMC Pre-NDA meeting on 17-OCT-2012:

- FDA reminded the sponsor to obtain a USAN for the drug substance.
- The sponsor clarified that the drug product is an immediate release capsule [(b) (4)]
- FDA agreed:
  - that the starting material of the drug substance is the [(b) (4)] fish oil
  - that the control of environmental pollutants in the intermediate is acceptable
  - that the attributes in the drug substance and drug product specifications are acceptable
  - that [(b) (4)] testing is not required in the drug product specification
  - with the proposed stability data package in the initial NDA submission for filing
  - with the proposed bulk product [(b) (4)] studies
  - with the justification for [(b) (4)] limits
  - with the proposed comparability protocols for [(b) (4)] to be filed as CBE-30 supplements with a current GMP compliance statement and 6-month of stability data for 3 batches.

Critical CMC Issues or Complexities (note issues or if there are none)

- The applicant requests that the new product be reviewed as a New Molecular Entity (NME). However, the new product includes the free acids of the two major active moieties (in ester form) of the approved product Lovaza (different applicant). They are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Compared to the approved labeling of Lovaza, the new product contains 500-600 mg/g of EPA (vs. 465 mg/g EPA-ethyl ester in Lovaza) and 150-250 mg/g DHA (vs. 375 mg/g DHA-ethyl ester in Lovaza). It is noted that DPA is a very minor component [(b) (4)] in Lovaza while it has a limit of [(b) (4)] mg/g in the new product.
- The dosage strength is 1000 mg omefas/capsule (measured as [(b) (4)] content weight per capsule, not including the capsule shell weight). The drug substance omefas is stated to be a mixture of polyunsaturated free fatty acids including multiple omega-3 and omega-6 fatty acids. Analytical data from 21 lots (including clinical and nonclinical lots) show the consistent presence of [(b) (4)] omega-3 fatty acids and [(b) (4)] omega-6 fatty acids, and the applicant proposes this [(b) (4)] peak profile to be the "fingerprint" of the drug substance:

  [(b) (4)]

  The drug substance specification includes acceptance criteria of "NLT 850 mg/g" of polyunsaturated free fatty acids, "[(b) (4)] mg/g" of total omega-3 fatty acids, "NMT [(b) (4)] mg/g" of total omega-6 fatty acids, among others. Based on current knowledge of other approved fish oil products, the reviewer will determine whether the proposed dosage strength is appropriate. Input from the Clinical team will be obtained on the identity of the active components in the mixture in order to assign the appropriate dosage strength to the product (i.e., the dosage strength should correlate with the content of the active components)

Does the submission contain any of the following elements?

Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	No

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marketing Applications

Is a team review recommended?		
Yes	No	Suggested expertise for team
x		Biopharmaceutics – review by Houda Mahayni

Summary or Highlights of the Application ***(not already mentioned in other sections)***

- The NDA is a 505(b)(1) application for a mixture of polyunsaturated free fatty acids derived from fish oil.
- The OPS Microbiology Staff indicated on 10-JUL-2013 that no Microbiology assignment is necessary and that the NDA is acceptable from the Microbiology standpoint (see attached email at the end of this review).

Drug Substance. All CMC information on the drug substance is included in the NDA.
Established name. The proposed established name for the drug substance is "omefas", which does not appear in the USP Dictionary. The sponsor was reminded by FDA at the CMC Pre-NDA meeting on 17-OCT-2012 to obtain an established name for the drug substance. The applicant states that the name request was sent to the USAN Council. See the 74-day letter comment on this issue.
Starting materials. The fish oil starting material is consistent with the starting material of other approved fish oil drugs, and this designation was agreed upon by FDA at the CMC Pre-NDA meeting on 17-OCT-2012.
Manufacture of the drug substance. Fish oil is (b) (4) As agreed upon by FDA at the CMC Pre-NDA meeting on 17-OCT-2012, several quality attributes are controlled (b) (4), for example: (b) (4). (b) (4) is added to the drug substance with acceptance criteria of (b) (4)% in the drug substance specification. The reviewer will determine whether the criteria are adequate to ensure stability of the drug substance over the proposed retest period.
Drug substance specification. The specification is copied at the end of this review. Justification is provided for the omission of testing for potential impurities such as residual reagent/solvent. All testing attributes were agreed upon by FDA at the CMC Pre-NDA meeting on 17-OCT-2012. The reviewer will determine appropriate acceptance criteria based on all available data, including data of nonclinical and clinical batches, and stability data. It is noted that the acceptance criteria for peroxide, p-anisidine, total oxidation, unsaponifiable matter, absorbance, cholesterol, and oligomers are based on the USP monograph for "omega-3 acid ethyl esters". This product does not have impurities in the usual definition for a small synthetic drug. For this product, many "impurities" are product-related substances, for example: (b) (4)
Input from the Pharmacology Toxicology team will be requested on these limits and on the limit of (b) (4) ppm on (b) (4), a side reaction product.
Packaging and stability. Information is provided on the container closure system of the drug substance (b) (4)
Primary stability data include up to 24 months at room temperature and 6 months under accelerated conditions for three drug substance batches manufactured by the commercial process at the commercial site, at (b) (4)% commercial scale.

Drug Product

Composition. A copy of the drug product composition is attached at the end of this review. There is no novel/non-compendial excipient. It is noted that the drug substance (b) (4)) is filled into the capsule shell (b) (4). The capsule has a coating consisting of ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4)%, which is used to (b) (4) (b) (4) This issue will be discussed with the Biopharmaceutics team.

Gelatin. The capsule shell gelatin is porcine-derived, thus eliminating the BSE/TSE risk.

Comparability of the product used in the clinical studies, stability studies, and commercial product. The applicant states that the formulation and manufacturing process are the same for all clinical and stability batches and the commercial product.

Product manufacture. The manufacturing process is standard for a soft gelatin capsule with the (b) (4). There are (b) (4) steps in the process: (b) (4). Information is provided on the process development, including a quality target product profile and risk assessment of the variables and unit operations.

Degradation products.

The applicant states that the primary oxidation is measured as peroxide and absorbance values, and the secondary oxidation as p-anisidine and total oxidation values. It is noted that the acceptance criteria for the following tests are based on or are the same as in the USP monograph for "Omega-3 Acid Ethyl Esters Capsules": absorbance, peroxide, p-anisidine, total oxidation, oligomers, and microbial limits.

(b) (4) with a limit of (b) (4)% in the drug product specification. In addition to the input from the Pharmacology Toxicology team on the safety of this limit, the reviewer will evaluate the (b) (4) data from clinical batches and obtain input from the Clinical team on the impact of (b) (4)% (b) (4) on efficacy. The applicant references literature for information on the in vivo digestion of (b) (4) and their relative bioavailability compared to the free fatty acid forms.

Uniformity of dosage units. This testing is the measurement of weight variation of the capsule content (not including the weight of the capsule shell).

Drug release. The proposed Capsule Rupture test and acceptance criteria will be evaluated by the ONDQA Biopharmaceutics team.

Container closure systems. The drug product will be packaged in 60-count HDPE bottles and 6-count aluminum blisters. The applicant states that the safety of the product-contact packaging components is shown by compliance to the indirect food additives regulations (21 CFR 177 and 174-186). Applicable USP testing per <671> and <661> was conducted. Compatibility is shown by stability data. The reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for oral drug products.

Stability. Sufficient stability data are provided in the submission for filing. The bottles have 36-month long-term data for one primary batch and 18-month long-term data for two primary batches. The blisters have 24-month long-term data for one primary batch and 3-month long-term data for a second batch. All batches were manufactured at the commercial site using the commercial process at greater than (b) (4)% of commercial scale. In addition, stability data are provided in support of a holding time of (b) (4) months for the (b) (4) and a holding time of (b) (4) months for the (b) (4) It is noted that, in addition to the formation of (b) (4) resulting from (b) (4), an (b) (4) was observed during the stability study, more significantly under accelerated conditions. The (b) (4) is explained to be the interaction between the (b) (4)

(b) (4). The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data. The applicant claims that the coated capsules packaged in the commercial bottles or blisters are adequately (b) (4) which will be verified by the reviewer.
Description of Any Facility Related Risks or Complexities with this Application.
See EES for complete list of facilities related to this application.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
4.	Is the CMC section organized adequately?	x		
5.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
6.	Are all the pages in the CMC section legible?	x		
7.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
8.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		

9.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	x		

	Parameter	Yes	No	Comment
10.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
11.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

Reference ID: 3360198

	Parameter	Yes	No	Comment
12.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
13.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
14.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
15.	Does the section contain a description of the DS manufacturing process?	x		
16.	Does the section contain identification and controls of critical steps and intermediates of the DS	x		
17.	Does the section contain information regarding the characterization of the DS?	x		
18.	Does the section contain controls for the DS?	x		
19.	Has stability data and analysis been provided for the drug substance?	x		
20.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
21.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
23.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
24.	Is there a batch production record and a proposed master batch record?	x		
25.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
26.	Have any biowaivers been requested?		x	
27.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
28.	Does the section contain controls of the final drug product?	x		
29.	Has stability data and analysis been provided to support the requested expiration date?	x		
30.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
31.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

Reference ID: 3360198

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
32.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
33.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			N/A

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE
(b) (4)	III		(b) (4)	15-MAR-2013
	III			13-MAR-2013
	IV			15-APR-2013

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
35.	Has the draft package insert been provided?	x		
36.	Have the immediate container and carton labels been provided?	x		

See appended electronic signature page}
CMC-Lead or CMC Senior Reviewer
Division
Office of New Drug Quality Assessment

{See appended electronic signature page}
Branch Chief or Designee
Division
Office of New Drug Quality Assessment

Reference ID: 3360198

Appendix 1. Composition of Drug Product

Table 2.3.P-1. Drug Product Composition			
Ingredient	**Function**	**Specification**	**Weight Per Capsule (mg)**
Omefas [a]	Active ingredient	*3.2.S.4.1*	1,000
Capsule Shell			(b) (4)
Gelatin (porcine type A, (b) (4) (b) (4))	Capsule shell	USP/NF, Ph. Eur.	
Sorbitol (b) (4)	(b) (4)	USP/NF, Ph. Eur.	
Glycerol (b) (4) %		Ph. Eur	
Purified Water		USP/NF, Ph. Eur.	
Total shell weight			
Capsule Coating			
Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4) %	(b) (4)	NF, Ph. Eur., JP	
Talc	(b) (4)	USP/NF	
Titanium dioxide		USP/NF	
Iron oxide red		USP/NF	
Polysorbate 80		USP/NF	
Carboxymethylcellulose sodium		USP/NF, Ph. Eur.	
(b) (4)		USP, Ph. Eur.	
Total coating weight			
Printing Ink [d]	Identification	USP/NF	
Total capsule weight			1,470.0

[a] = Omefas contains (b) (4)
[b] =
[c] =
[d] = The qualitative composition of the ink is provided in *Table 3.2.P.1-2*
[e] = (b) (4)

Appendix 2. Drug Product Specification

Table 2.3.P-4. Drug Product Release and Shelf-life Specifications				
Test Parameter	Acceptance Criteria		Test Method	Stability Indicating
	Release	Shelf Life		
Identity				
Appearance Capsule exterior Capsule content	 Red/ brown coated gelatin capsule with "OME1" printed in white Clear yellow to amber oil		OP6.1065	Yes
Identification, GC	Conforms to profile requirement [a]	N/A	OP6.1071	No [b]
Purity				
Acid Value (AV)	(b) (4) mg KOH/g	(b) (4) mg KOH/g	OP6.1047	Yes
Peroxide Value (PV)	NMT (b) (4) meq/kg	NMT (b) (4) meq/kg	OP5.3004	Yes
p-Anisidine Value (pAV)	NMT (b) (4)	NMT (b) (4)	OP5.4050	Yes
Total Oxidation Value (TOTOX)	NMT (b) (4)	NMT (b) (4)	Calculation (2xPV+pAV)	Yes
Absorbance	NMT (b) (4)	NMT (b) (4)	OP5.4051	Yes

Table 2.3.P-4. Drug Product Release and Shelf-life Specifications				
Test Parameter	Acceptance Criteria		Test Method	Stability Indicating
	Release	Shelf Life		
Strength				
Fatty Acid Composition				
Polyunsaturated Free Fatty Acids [c]	NLT 850 mg/ capsule		OP6.1071	Yes
EPA	500 to 600 mg/ capsule			
DHA	150 to 250 mg/ capsule			
EPA + DHA	(b) (4) mg/ capsule			
Total Omega-3	mg/ capsule			
Quality				
Uniformity of mass of single dose	NMT (b) (4) individual capsule contents deviate from the average weight by more than ± (b) (4) % and none deviates by more than (b) (4) %.	N/A	OP6.1063	No
Average mass of contents	(b) (4) mg/capsule	N/A	OP6.1063	No
Average mass of capsules	(b) (4) mg/capsule	N/A	OP6.1063	No
Loss on Drying (Water in shell)	(b) (4) % m/m	(b) (4) % m/m	OP5.5019	Yes
Oligomers	NMT (b) (4) % a/a		HMR/2K/M619	Yes
Total Glycerides	NMT (b) (4) % a/a	NMT (b) (4) % a/a	HMR/2K/M619	Yes
α-Tocopherol	(b) (4) % w/w		OP6.1068	Yes
Omefas release (Quantitative capsule rupture test)			OP6.1083	Yes
30 minutes	(b) (4)			
120 minutes				

Table 2.3.P-4. Drug Product Release and Shelf-life Specifications				
Test Parameter	Acceptance Criteria		Test Method	Stability Indicating
	Release	Shelf Life		
Microbial Limits				
Total aerobic count	NMT (b) (4) CFU/g		HMR/2K/M57	Yes
Total yeast and mold count	NMT CFU/g			
Escherichia coli	Absent (b) (4) g		HMR/2K/M58	
Salmonella	Absent/ (b) (4) g			

[a] = The qualitative identity of Epanova is defined as the presence of (b) (4) (b) (4)

[b] = Identification is not stability indicating in and of itself and must be considered with the total output of the fatty acid composition analysis

[c] = Polyunsaturated free fatty acids include omega-3, omega-6 and other polyunsaturates

[d] = (b) (4)

NLT = Not less than
NMT = Not more than
N/A = Not applicable

Appendix 3. Drug Substance Specification

Table 2.3.S-7. Drug Substance Specifications			
Test Parameter	**Acceptance Criteria**	**Test Method ID**	**Stability Indicating**
Identity			
Appearance	Clear yellow oil	Visual assessment	Yes
Identification, GC	Conforms to profile requirements[1]	*QCTM0194*	No
Purity			
Acid Value	(b) (4) mg KOH/g	*QCTM0198*	Yes
Saponification Value	mg KOH/g	*QCTM0199*	No
Ester Value	NMT (b) (4) mg KOH/g	Calculation	No
Peroxide Value	NMT (b) (4) meq/kg	*QCTM0192*	Yes
p-Anisidine Value	NMT (b) (4)	*QCTM0193*	Yes
Total Oxidation Value (TOTOX)	NMT	Calculation	Yes
Unsaponifiable matter	NMT (b) (4) % (w/w)	*QCTM0202*	No
Absorbance	NMT	*QCTM0197*	Yes
Cholesterol	NMT mg/g	*QCTM0206*	No
Oligomers	NMT % (a/a)	*QCTM0257*	No[2]
(b) (4)	NMT ppm	*TP66980*	No
Strength			
Fatty Acid Composition: Saturated Free Fatty Acids			
Polyunsaturated Free Fatty Acids	NLT 850 mg/g	*QCTM0194*	Yes[4]
EPA	500-600 mg/g		
DHA	150-250 mg/g		
DPA	(b) (4) mg/g		
EPA+DHA	(b) (4) mg/g		
Total Omega-3 Fatty Acids	mg/g		
Total Omega-6 Fatty Acids	NMT (b) (4) mg/g		
Other Polyunsaturated Fatty Acids	NMT (b) (4) mg/g		

[redacted]	NMT [redacted]% (a/a)		
[redacted]	NMT [redacted]% (a/a)		
Quality[5]			
[redacted]	[redacted]%	*QCTM0285*	Yes

[1] = The qualitative identity of omefas is defined as presence of [redacted]

[2] =

[3] =

[4] =

[5] = As agreed to in the pre-NDA meeting microbial limits is maintained for stability only (pre-NDA CMC meeting documented in *Sponsor's meeting minutes* in *Section 1.6.3*) as microbial limits is performed for drug product release.

From: CDER OPS IO MICRO
To: Tran, Suong T; Christodoulou, Danae D; McKnight, Rebecca; CDER OPS IO MICRO; Dorantes, Angelica
Cc: Riley, Bryan S
Subject: RE: new NDA 205060 for omefas capsules
Date: Wednesday, July 10, 2013 1:23:23 PM

This submission is acceptable from a product quality microbiology standpoint and will be recommended for approval Therefore, no product quality microbiology reviewer assignment will be made for this submission. A review memo describing the assessment of the microbial controls for the drug product will be entered into DARRTS.

Thanks, Vera

-----Original Message-----
From: Tran, Suong T
Sent: Wednesday, July 10, 2013 10:39 AM
To: Christodoulou, Danae D; McKnight, Rebecca; CDER OPS IO MICRO; Dorantes, Angelica
Subject: new NDA 205060 for omefas capsules
Importance: High

Application Number: NDA 205060
Product Established Name: omefas
Dosage form: soft capsule for oral administration
Submission received date: 05-JUL-2013
OND RPM: Kati Johnson
ONDQA RPM: Rebecca McKnight
Clinical Division: Metabolism/Endocrinology

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

/s/

SUONG T TRAN
08/20/2013

DANAE D CHRISTODOULOU
08/20/2013