

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205060Orig1s000**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: April 14, 2014

To: Jean-Marc Guettier, MD  
Acting Director  
**Division of Metabolism and Endocrinology Products  
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

From: Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
  
Ankur Kalola, Pharm.D.  
Consumer Safety Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): EPANOVA (omega-3-carboxyl acids)

Dosage Form and Route: Capsules

Application Type/Number: NDA 205060

Applicant: Astra-Zeneca

## 1 INTRODUCTION

On July 5, 2013, Omthera Pharmaceuticals, submitted for the Agency's review a New Drug Application for EPANOVA (omefas) Capsules indicated as an adjunct to diet to reduce triglyceride, (b) (4) levels in adult patients with severe hypertriglyceridemia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on September 16, 2013 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for EPANOVA (omega-3-carboxyl acid) Capsules.

On December 31, 2013, the Agency was notified of the transfer of ownership for this NDA from Omethera Pharmaceuticals to Astra-Zeneca and a change in established name for EPANOVA from "omefas" to "omega-3-carboxyl acid". Revised labeling for EPANOVA was submitted on that date.

## 2 MATERIAL REVIEWED

- Draft EPANOVA (omega-3-carboxyl acid) Capsules PPI received on December 31, 2013 and received by DMPP on January 6, 2014
- Draft EPANOVA (omega-3-carboxyl acid) Capsules PPI received on December 31, 2013 and received by OPDP on January 6, 2014
- Draft EPANOVA (omega-3-carboxyl acid) Capsules Prescribing Information (PI) received on December 31, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on April 7, 2014
- Draft EPANOVA (omega-3-carboxyl acid) Capsules Prescribing Information (PI) received on December 31, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on April 7, 2014
- Approved LOVAZA (omega-3-acid ethyl esters) comparator labeling dated September 11, 2013

## 3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved Lovaza comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROBIN E DUER  
04/14/2014

ANKUR S KALOLA  
04/14/2014

SHAWNA L HUTCHINS  
04/14/2014

LASHAWN M GRIFFITHS  
04/14/2014

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**CLINICAL INSPECTION SUMMARY**

**DATE:** April 9, 2014

**TO:** Iffat Chowdhury, M.D., Clinical Reviewer  
James P. Smith, M.D., M.S., Clinical Team Leader  
Kati Johnson, Senior Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**FROM:** Cynthia F. Kleppinger, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 205060

**APPLICANT:** Omthera Pharmaceuticals, Inc.

**DRUG:** Epanova<sup>TM</sup>/ omega-3 carboxylic acids

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATIONS:** An adjunct to diet to reduce triglycerides, (b) (4)

(b) (4)  
 \_\_\_\_\_ levels in adult patients  
 with severe ( $\geq 500$  mg/dL) hypertriglyceridemia.

CONSULTATION REQUEST DATE: September 10, 2013  
 CLINICAL INSPECTION SUMMARY GOAL DATE: April 10, 2014  
 DIVISION ACTION GOAL DATE: May 1, 2014  
 PDUFA DATE: May 5, 2014

## I. BACKGROUND

Omthera Pharmaceuticals, Inc. is seeking approval of Epanova™ (omega-3 carboxylic acids) for the treatment of severe hypertriglyceridemia (TG >500 mg/dL). The application is based on the results of a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial M-EPA-003 entitled, "Efficacy and Safety of Epanova™ in Severe Hypertriglyceridemia (EVOLVE)." Although the pivotal trial EVOLVE was conducted with three doses of Epanova™ (2g, 3g, and 4g) as compared to placebo, the applicant proposed only the 2g and the 4g doses for final approval.

The first subject was screened April 4, 2011, and the last subject completed the study February 8, 2012. There were 74 centers that screened 1356 subjects and randomized 399 subjects.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 205060 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

## II. RESULTS (by Site)

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Pending Classification
Alexey Blokhin Site 133	OM-EPA-003 36 subjects	December 16-20, 2013	NAI
Marianna Zsom Site 109	OM-EPA-003 17 subjects	January 06-10, 2014	NAI
Zsolt Ples Site 105	OM-EPA-003 16 subjects	January 13-17, 2014	NAI
Mieke Trip Site 141	OM-EPA-003 10 subjects	January 20-24, 2014	NAI

Omthera Pharmaceuticals, Inc.	OM-EPA-003	October 16-18, 22-25, 30, November 5, 2013	VAI
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Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to the site.

**1. Alexey Blokhin, MD, PhD**

Federal State University  
Grokholsky Lane, 31  
Moscow, 129090  
Russia

- a. **What was inspected:** There was a 100% review of the subject informed consent forms (ICFs). There was a 50% review of records (all even numbered subjects) for inclusion/exclusion, adverse events and primary efficacy; the other half of the records (all odd numbered subjects) were reviewed for ECG and the “Therapeutics Lifestyles Changes (TLC) Compliance” diet. The Form FDA 1572 “Statement of Investigator” and financial disclosure information for the Principal Investigator and the financial disclosure documents for the investigator were reviewed. The local ethics committee and Russian Health Authority approval letters and correspondences were reviewed. Drug accountability, record storage and monitoring were reviewed.
- b. **General observations/commentary:** The site screened 45 subjects, 36 subjects were randomly assigned to study drug, and 16 subjects completed the per-protocol schedule. Five subjects (12, 27, 42, 43, 44) who were screened were discontinued for lack of study drug supply (reported as “per sponsor design”), and 20 subjects had premature Week 8 visits because of interrupted drug supply. These changes to the dosing and visit schedule were requested by the sponsor to accommodate the suspension of sample shipping resulting from national holidays. The records showed unanticipated high enrollment rate and low rate of screening failures which caused the final enrollment numbers to exceed the quantity of study drug available.

The records supported that the study protocol and the informed consent document were approved by the local ethics committee and the Russian Health Authority before any subject underwent any study-specific procedures. Dr. Blokhin personally obtained informed consent for all subjects. Two subjects did not sign and date the ICFs; protocol deviations were reported to the sponsor by the site monitor and to the local ethics committee by the investigator.

No under-reporting of adverse events was found. The investigator was blinded to the efficacy data; therefore, source efficacy data was not available at the site and were provided by the central laboratory electronically and by the sponsor post-inspection. Post-inspectional review of 100% of Week 7 and 8 data produced no deficiencies and the endpoint data was verifiable. Records supported that the wash-out occurred as required by the protocol. Record keeping and control over the site data was adequate; evidence reviewed supported that study drug was handled appropriately. A complete drug accountability review was done for one chart. All subjects were compliant with the TLC diet according to the records. There was adherence to the protocol with respect to use of prohibited medications.

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

## 2. Marianna Zsom, MD\*

Rókus utca 10  
Baja, 6500  
Hungary

\* The firm is located in the local hospital, Baja Szent Rokus Korhaz, but is a separate legal entity.

- a. **What was inspected:** All records (46) were reviewed for informed consent. Seventeen records were reviewed completely for inclusion/exclusion, adverse events, primary efficacy endpoint, and drug compliance. The correspondences and approvals from the ethics committee were reviewed as well as delegation of duties, 1572s, financial disclosure, drug accountability, randomization, training, monitoring, source documents and the electronic case report forms.
- b. **General observations/commentary:** There were 46 subjects screened, 17 subjects enrolled, and 14 who completed the study. The first subject was screened on 4/19/2011 and the last subject follow-up was 1/17/2012. The study was under approval of a local ethics committee and the Ethics Committee for Clinical Pharmacology at the National Institute of Pharmacy in Hungary. Records were organized and had adequate documentation. There was no evidence of under-reporting of adverse events. The primary efficacy endpoint data was verifiable. The triglyceride and cholesterol data was blinded at the site for Visits 5 through 8 so the source data was not at the site. These visits were

verified from central laboratory data provided by the sponsor. Data from Visits 1-4 were verified from source data. No discrepancies were found.

Protocol deviations were observed and had been previously reported. Per section 7.4 of the protocol, subjects being screened with abnormal laboratory values could be retested once. However, with the earlier subjects with high plasma glucose levels (021, 022, 025, 028), they were not retested prior to randomization. The subjects have protocol deviations recorded for not retesting and being allowed to continue (the failed exclusion was discovered by the monitor). These earlier subjects were retested sometime after randomization for plasma glucose (all with normal values). The sponsor sent an email saying that subjects with retested normal values were able to continue in the study (email sent after randomization).

There was one missing source document. The ECG for Subject 011 was documented as normal in the source record but the original ECG could not be found.

There were occasional, rare errors noted from the source to the eCRF and two instances where a box indicating if the subject was ok to continue was not checked. The most significant transcription error was the serious adverse event (SAE) for Subject 109011; it describes the severity level of the abdominal pain as mild in the eCRF and the report to the sponsor but the source documents describe the pain as moderate (it is correctly categorized as a serious adverse event). The CRFs were consistent with the data listings. These transcription errors were discussed with the site.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

### 3. Zsolt Ples, MD

Evolucio Betegellatasi Kozpunt\*  
Mártírok útja 9  
Sátorajjáújhely, 3980  
Hungary

\*At the time of the study, the research entity went by the name CEE Research Kft.

- a. **What was inspected:** All consent forms were inspected. The source records for all 16 subjects randomized as well as 15 screen failures were reviewed.

- b. General observations/commentary:** There were 66 subjects screened and 16 randomized/enrolled. All 16 completed the study. There were no issues with informed consents, the 1572s, financial disclosures, drug accountability or randomization. There was no under-reporting of adverse events. The primary efficacy endpoint data was verifiable. The triglyceride and cholesterol data was blinded at the site for Visits 5 through 8 so the source data was not at the site. These visits were verified from central laboratory data provided by the sponsor. Data from Visits 1-4 were verified from source data. No discrepancies were found.

Some minor issues found were discussed with site staff:

- An SAE of angina pectoris (Subject 028) was reported to the sponsor two days later and should have been reported within 24 hours per protocol.
- Subject 028 had a history of pancreatitis and should have been excluded from the study (medical monitor approved continuation in the study)
- Inclusion criteria protocol deviations (such as laboratory retested only at the local lab not via the central lab before randomization)
- A subject with diabetes should have had their HbA1c tested during Visit 1 but was not tested until Visit 2 (but was tested before randomization/receiving the study drug).
- Two subjects' Visit 1 dates were out of window. (Washout periods were not effected as the one subject with a shortened timeframe was taking a stable dose of statin).
- One subject (053) noted as not Hispanic in source and as Hispanic in CRF.
- Source Eligibility checklists completed during Visit 1 for three subjects were missing. In each case the checklist was complete for another visit.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**4. Mieke Trip, MD, PhD**

Academics Medical Center  
Dept of Cardiology and  
Vascular Medicine  
Meibergdreef 9  
Amsterdam, 1105 AZ  
Netherlands

- a. What was inspected:** All informed consents were inspected. All 10 randomized subjects and five screen failure records were reviewed. Informed consent procedures, 1572s, financial disclosure, screening and enrollment, monitoring, source documents, drug accountability, review of the eCRF, primary and secondary efficacy endpoint data, ethics committee correspondence and approval, the regulatory binder, delegation of duties, and correspondences between the sponsor and site were reviewed.
- b. General observations/commentary:** There were 19 subjects screened, 10 subjects randomized, and nine who completed the study. Consent was obtained from all before enrollment. The first subject was screened on 5/23/2011 and the last subject follow-up was 12/1/2011. Dr. Trip is a member of the ethics committee; all correspondence from the ethics committee noted this and stated that he did not participate in the consultation and decisions. Records were organized. There was no under-reporting of adverse events. After the study was closed this site requested and received by email from the sponsor the triglyceride data, and used this data to send subjects a follow-up letter about their participation in the study. The site also received a copy of the case report forms after database lock. Therefore, the data was available at the site for primary efficacy verification. There were no discrepancies.

During the inspection, it was noted that there were several (26) minor rounding errors noted. For example, blood pressure measurements of 135 and 140 have an average of 137.5 and this was rounded to 137.

There were some minor issues discussed with staff at close-out. Subject 007 at Visit 4 and Subject 012 at Visit 8 did not have their weight taken as required by the protocol. There were also several out of window visits for Subjects 002, 011 and 013. Subject 013 had a box checked for an adverse event at Visit 7 but nothing was noted in the source record until 10 days later.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted

data.

## 5. Omthera Pharmaceuticals

c/o Dr. Michael Davidson, Executive Vice President  
707 State Road  
Princeton, NJ 08540

- a. What was inspected:** Organizational structure and personnel, training, and job qualifications of the monitors and site personnel, selection and monitoring of clinical investigations, contractual agreements for contract research organizations (CROs), written Standard Operating Procedures (SOPs), monitoring procedures, monitoring reports, quality assurance (QA), protocols, informed consent forms, registration of studies on ClinicalTrials.gov, safety reporting, data verification of adverse events and efficacy endpoints, FDA 1572s, data collection and handling, financial disclosure, electronic records and signatures, and investigational product integrity and accountability were reviewed.
- b. General observations/commentary:** Currently Omthera is composed of 14 employees and has been at its current site since December 2011. During the study, Omthera contracted (b) (4), which subcontracted (b) (4) for monitoring the clinical sites in Europe. (b) (4) subcontracted (b) (4) to provide monitoring for the clinical sites in India. (b) (4) also was responsible for subcontracting and managing the other CROs, such as (b) (4). The sponsor did not have a QA unit during the conduct of the study and during the inspection the sponsor did not have any approved SOPs related to QA.

Training records were reviewed for the investigators, clinical monitors and study coordinators for the inspected sites and appeared adequate. There was a protocol dated 4/27/2011 "India version" that was identical to the protocol in the assignment except that it included subjects between 18 to 65 years of age (as opposed to  $\geq 18$  years of age in the protocol). This was approved by the Office of Drugs Controller General India (DCGI).

The protocol OM-EPA-003 was registered in ClinicalTrials.gov; the task delegated to (b) (4) (b) (4) did not have an SOP for this task. In reviewing the website, not all the secondary outcome measures were listed. The date of last subject completion was 2/8/2012. Therefore, the required informed consent language was not in the consents.

The majority of the investigators were recommended by the CRO (b) (4). Some of the qualification visits were done by telephone and with new investigators, which was against (b) (4) SOP. All signed 1572s were reviewed and appeared adequate. The sponsor

contracted (b) (4) to obtain financial disclosure information from each clinical investigator. The financial disclosure information was obtained only before the investigator's participation in the study and it was not obtained one year after study completion.

For the inspected sites, all PIs received the necessary information such as protocols, investigator's brochures, and labeling prior to study initiation. There were no clinical investigator sites where the study conduct was terminated. One Indian site (Dr. Pai/Site 205) had to be brought into compliance. The sponsor reviewed all the monitoring reports but did not document these reviews.

All adverse events in the CRFs for the inspected sites were reviewed and no deficiencies were found. SOPs for safety reporting were reviewed and appeared adequate.

An electronic data capture, which documented an audit trail, was used for the study. However, a data verification form was not used for the study. Corrections to CRFs were done with confirmation or verification from the investigator or study coordinator when changes were made, and this process was documented on the audit trials.

In the protocol, glucose was to be drawn at two visits, Visit 2 (Week -2) and Visit 8 (Week 12). However, during the inspection it was noted that in Section 16.2.8.1 in the data listings for some subjects there are two Visit 2 glucose values. For example, for Subject 109-022, the data line listings have V2 glucose 213 on 8/2/2011 and V2 glucose 267 on 8/16/2011. The sponsor was asked to clarify and said that for programming specifications, "Visit 2: Week -2" applied to any visit on or before randomization and "Visit 8: Week 12" applied to any visit after randomization. Therefore, if a patient had glucose data from two visits prior to randomization, they would both be called "Visit 2: Week -2." The programming for the listings from Section 16.2.8.1, required use of the "Analysis Visit" data unless the "Visit Number" was "999" then that visit was called "Unscheduled." For the analysis, the programming specified that the visit closest to the target date should be used in the analysis. The glucose levels at all visits for all randomized subjects at the four sites were verified and appeared as described.

The sponsor learned in early December that most sites and customs office would be closed in Russia from Dec 28, 2011 to Jan 8, 2012 for the holidays. Therefore sponsor staff worked with sites to schedule patients to avoid interrupting study medications and be sure that laboratory samples could be shipped to the central laboratory.

At the conclusion of the inspection, a Form FDA 483 was issued for the following:

**OBSERVATION 1** Failure to ensure the study was conducted in accordance with the protocol and/or investigational plan. Specifically,

- A. The protocol was not always followed during the conduct of the study at Site 109 where a total of 17 subjects were randomized. For example, the following subjects were included to participate in the study despite meeting #18 exclusion criteria which states “Any of the following laboratory criteria...fasting serum glucose > 200 mg/dL or platelet count <  $60 \times 10^9/L$ .”
1. Site 109: Four subjects (021, 022, 025, 028) were randomized and received investigational products despite having fasting serum glucose > 200 mg/L. Three of these subjects completed the study.

**OSI Comment:** Protocol deviation forms for these subjects were completed 35-56 days after randomization. The Medical Monitor’s response was “...repeat glucose at next visit...Not a safety issue since the HbA1C is within range”. Eligibility should have been reviewed sooner. Omthera responded and acknowledged the finding. To prevent instances in the future, the Interactive Web Response System (IWRS) will be programmed to not permit a subject to be randomized into the study if they meet any of the laboratory exclusion criteria. If IWRS is not employed, additional training, instruction, and ongoing monitoring will be conducted.

2. Site 109: One subject was randomized, received IPs, and completed the study; however, this subject’s platelet count was not measured prior to randomization. Additionally, this subject’s platelet count was not measured until Visit 8/Week 12 (end of study).

**OSI Comment:** The hematology laboratory report documented “platelet clumps”. This should have been repeated. The site monitor never mentioned that this laboratory test was never done. A protocol deviation form was not completed at the site. . Omthera responded and acknowledged the finding. To prevent instances in the future, the Interactive Web Response System (IWRS) will be programmed to not permit a subject to be randomized into the study if they meet any of the laboratory exclusion criteria. In addition, more emphasis will be placed on the importance of using the protocol specified laboratory. If IWRS is not employed, additional training, instruction, and ongoing monitoring will be conducted.

- B. According to section 7.11 “Safety Laboratory Assessments and Procedures” of the protocol, dated January 31, 2011, “all safety laboratory analyses, other than urine pregnancy tests, will be performed by a central laboratory or a specialized facility; however, the safety laboratory analyses for 3 out of 16 randomized subjects at site 105 were

performed by the clinical investigator's local laboratory. Additionally, these safety laboratory analyses were used to evaluate exclusion criterion #18 of the protocol.

**OSI Comment:** Subjects 105029 and 105034 had exclusionary serum glucose levels that were repeated and reported to be normal by the local laboratory. This was not picked up by the monitor until towards the end of the study. Subject 105053 had a clotted specimen for hematology and platelets at Visit 2 but normal results through the local laboratory and was randomized. This deviation was not picked up by the monitor until close of the study. Omthera responded and acknowledged the finding. To prevent instances in the future, the Interactive Web Response System (IWRS) will be programmed to not permit a subject to be randomized into the study if they meet any of the laboratory exclusion criteria.

- C. According to section 5.2 "Investigational Product Storage and Accountability" of the protocol, dated January 31, 2011, "the Principal Investigator (PI) or designee will inventory and acknowledge receipt of all shipments of investigational product". However, seven out of 10 IP shipments at Site 141 were received by three different individuals who were not authorized to receive the IPs.

**OSI Comment:** The "Study Personnel Delegation of Tasks Log" failed to include the names of these individuals. These individuals were also not listed on the FDA 1572. Omthera responded and acknowledged that seven out of 10 IP shipment receipt forms at Site 141 were signed by three different individuals who were not delegated this responsibility. The institution's procedures for delegation of tasks for study related IP states that for each study a hospital pharmacist is assigned as the responsible person and can sign the study specific delegation logs. The three individuals were pharmacy assistants. In the future, the sponsor will train all individuals and CRO staff that those who are involved with the study protocol must be listed on the delegation log.

**OBSERVATION 2** Shipment of an investigational new drug to someone not an investigator participating in the investigation. Specifically, the investigational products were shipped to an individual who was not listed in the Statement of Investigator, Form FDA 1572, or "Study Personnel Delegation of Tasks Log". For example, all shipment records at Site 105 included the name of this individual to whom the investigational products were shipped.

**OSI Comment:** The records also failed to list Dr. Ples' name. Omthera responded and acknowledged the finding. The person who received the shipment was the study coordinator during the qualification and initiation visits but then left before the actual study began so was not on the delegation log. The system was also not updated regarding removal of the person's name. In the future, the sponsor will train all individuals and CRO staff that those who are

involved with the study protocol must be listed on the delegation log. In addition, all future investigational product shipments will be addressed to the investigator.

**OBSERVATION 3** Lack of adequate records covering receipt, shipment to investigators, and disposition of investigational drugs

Specifically, you failed to maintain adequate records showing the name of the investigator to whom the investigational products were shipped and the quantity of investigational products destroyed. For example,

- A. All shipment and receipt records at Site 141 failed to include the name of the investigator to whom the investigational products were shipped.

**OSI Comment:** As noted in 21 CFR 312.57 Recordkeeping and record retention. *(a) A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.* Omthera responded and acknowledged the finding. The company has informed the IP distribution vendor of the observation and it has agreed that all future investigational product shipments will include the investigator's name in addition to the pharmacist (if applicable).

- B. The investigational product disposition record "Drug Destruction Form" dated 1/18/2013 for Site 133 failed to include the quantities of investigational products destroyed.

**OSI Comment:** Omthera responded and acknowledged the finding. Drug accountability was verified and documented by the monitor prior to drug destruction. In the future, Omthera will require documentation of dual accountability, inclusive of the quantities of investigational product, prior to drug destruction.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, the audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this sponsor appear acceptable.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections for this NDA included four foreign clinical sites as well as the sponsor.

Observations noted above for all sites and the sponsor are based on the preliminary review of the Establishment Inspection Reports. An inspection summary addendum will be generated if

conclusions change upon OSI final classification.

All four clinical sites, Drs. Blokhin (Site 133), Zsom (Site 109), Ples (Site 105) and Trip (Site 141), were not issued a Form FDA 483; classifications for each of these inspections are NAI (No Action Indicated). Data from these sites are considered reliable based on the available information.

The sponsor was issued a Form FDA 483 citing inspectional observations and classification for the inspection is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data in support of this application may be considered reliable based on available information.

In general, based on the inspections of the four clinical study sites and the sponsor, the inspectional findings support validity of the data as reported by the sponsor under this NDA.

*{See appended electronic signature page}*

Cynthia F. Kleppinger, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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/s/  
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CYNTHIA F KLEPPINGER  
04/09/2014

JANICE K POHLMAN  
04/10/2014

KASSA AYALEW  
04/10/2014

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** April 8, 2014

**To:** Kati Johnson, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Ankur Kalola, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** OPDP Labeling Consult Request

NDA 205060 EPANOVA® (omega-3-carboxylic acids) capsules, for oral use

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On September 16, 2013, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) and Patient Information (PPI) for Epanova. OPDP's comments on the proposed draft PI for Epanova are based on the version sent via email from Kati Johnson on April 7, 2014.

OPDP's comments on the PI are provided directly on the marked version below.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the PPI under separate cover.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or [Ankur.Kalola@fda.hhs.gov](mailto:Ankur.Kalola@fda.hhs.gov).

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/s/  
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ANKUR S KALOLA  
04/08/2014

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 205060

**Application Type:** New NDA

**Name of Drug/Dosage Form:** Epanova (omega-3 carboxylic acid) Capsules

**Applicant:** Astra Zeneca

**Receipt Date:** July 5, 2013

**Goal Date:** May 5, 2014

## 1. Regulatory History and Applicant's Main Proposals

Epanova is the fourth fish oil application submitted for marketing. There are currently two approved products: Lovaza (omega-3-acid ethyl esters)[NDA 21654] and Vascepa (icosapent ethyl)[NDA 202057]. There is also a pending NDA, Omtryg (NDA 204977). All of the approved and pending fish oil products are indicated for the treatment of severe hypertriglyceridemia ( $TG \geq 500$  mg/dL), which has been implicated as a cause of acute pancreatitis. To obtain an indication for [REDACTED] (b) (4), with concomitant statin use, current division policy is to have an ongoing cardiovascular outcomes trial (CVOT) with 50% of patients enrolled before an applications would be filed.

The sponsor submitted a CVOT protocol, *A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia* (STRENGTH) on August 31, 2011. A "SPA Agreement" letter was issued March 16, 2012. The study has yet to be initiated.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

Minor SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix. These labeling deficiencies will be addressed during labeling negotiations.

# Selected Requirements of Prescribing Information

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## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

## Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

## Selected Requirements of Prescribing Information

### Comment:

#### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *The date will be added prior to approval.*

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

#### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

#### Indications and Usage in Highlights

**YES**

## Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

### Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *This date will be inserted prior to approval*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:** *Does not reference the type of FDA-approved patient labeling. The firm will be requested to add "See FDA-approved Patient Labeling (Patient Information)*

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

- [text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

#### 6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

#### 7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

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

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/s/  
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KATI JOHNSON  
02/19/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: December 12, 2013

Reviewer: Michelle K. Rutledge, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Epanova (Omega-3-Carboxylic Acids) Capsules, 1 gram

Application Type/Number: NDA 205060

Applicant/sponsor: Omthera Pharmaceuticals/AstraZeneca

OSE RCM #: 2013-1648

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## Contents

1	INTRODUCTION .....	1
1.1	Background .....	1
1.2	Product Information.....	1
2	METHODS AND MATERIALS REVIEWED .....	1
2.1	Labels and Labeling .....	1
3	CONCLUSIONS .....	2
4	RECOMMENDATIONS.....	2
	Appendices.....	4

## 1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, and prescribing information for Epanova (Omega-3-Carboxylic Acids) Capsules (NDA 205060) for areas of vulnerability that could lead to medication errors.

### 1.1 BACKGROUND

This New Drug Application 205060 for Epanova (Omega-3-Carboxylic Acids) Capsules was submitted on July 5, 2013.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the July 5, 2013 of the NDA submission.

- Active Ingredient: Omega-3-Carboxylic Acids
- Indication of Use: a lipid-altering agent, indicated as an adjunct to diet to reduce triglyceride (TG), [REDACTED] (b) (4) levels in adult patients with severe ( $\geq 500$  mg/dL) hypertriglyceridemia.
- Route of Administration: Oral
- Dosage Form: soft gelatin capsules
- Strength: 1 gram
- Dose and Frequency: 2 grams (2 capsules) daily as a single dose
- How Supplied: Bottles of 60 capsules
- Storage: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)
- Container and Closure System: Packaged in white, opaque high density polyethylene (HDPE) bottles. The closures are [REDACTED] (b) (4) [REDACTED] screw caps with [REDACTED] (u) (4). In addition, the capsules may be blister packaged in units of aluminum/aluminum foil for physician samples. The individual blister sheet may be packaged as an individual blister card. The drug product will be packaged using materials, which are approved for food packaging or direct food use per the regulations and used for approved drug products.

## 2 METHODS AND MATERIALS REVIEWED

### 2.1 LABELS AND LABELING REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 31, 2103 (Appendix A)
- Carton Labeling submitted December 31, 2013 (Appendix B – Appendix D)
- Prescribing Information submitted December 31, 2013 (no image)

### 3 CONCLUSIONS

DMEPA concludes that the proposed Prescribing Information labeling is acceptable.

DMEPA concludes that the proposed container labels and carton labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

### 4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

#### 4.1 COMMENTS TO THE APPLICANT

##### A. COMMERCIAL SIZE BOTTLE LABEL

1. Per FDA's Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors Guidance, we recommend deleting the (b) (4) is prominent, adds clutter to the principal display panel, and distracts the reader's attention for the important information, such as product's name and strength<sup>2</sup>.
2. We recommend deleting the (b) (4)  
[REDACTED]  
Therefore, this statement is unnecessary and adds to the clutter on the principal display panel and does not qualify as a unique circumstance which designates being highlighted on labeling.
3. Relocate the strength of the product away from the net quantity to help avoid misinterpretation of the strength as the net quantity.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

<sup>2</sup> <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm331808.htm>  
[[Accessed January 22, 2014]]

4. Add a warning statement to the principal display panel: “Swallow capsule whole. Do not break, open, crush or chew” because the availability of the product is affected if the capsule is not intact.
5. Consider using a capital case ‘E’ for the proprietary name to increase the readability of the proprietary name.

#### B. PROFESSIONAL SAMPLES BLISTER PACK LABEL

1. See A1 through A5 and revise sample blister pack label accordingly.
2. Revise strength statement per capsule (i.e., 1 gram per capsule).
3. Reduce prominence of Rx only statement by decreasing font size and debolding to help emphasize the most important information on the label such as product’s name and strength.

#### C. PROFESSIONAL SAMPLE BLISTER CARTON LABELING

1. See A1 through A5 as well as B2 and revise sample blister carton labeling accordingly.
2. Per FDA’s Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors Guidance, we recommend removing the large watermark graphic from the label as this graphic is prominent, adds clutter to the principal display panel, and distracts the reader’s attention for the important information, such as product’s name and strength<sup>2</sup>.
3. If space permits, revise the strength statement to include per capsule on the side panels on the carton labeling, such as 1 gram per capsule.

#### D. PROFESSIONAL SAMPLE BLISTER CARTON DISPLAY CASE LABELING

1. See A1 through A5 as well as B2 and revise sample blister carton display case labeling accordingly.
2. In addition, revise quantity to read “6 capsules per pack. 6 packs Total” to increase clarity of quantity of samples in display case.

If you have further questions or need clarifications, please Terrolyn Thomas, Project Manager, at 240-402-3981.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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MICHELLE K RUTLEDGE  
01/30/2014

YELENA L MASLOV  
01/30/2014



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 14, 2013

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Kathy Johnson, RPM  
DMEP

Subject: QT-IRT Consult to NDA 205060

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated September 16, 2013 regarding Cardiac Safety Report. The QT-IRT received and reviewed the following materials:

- Your consult
- TQT waiver request consult review under IND 107616 (July 19, 2012; September 24, 2012)

## QT-IRT Comments for DMEP

We reviewed the sponsor's submission and concluded that ECG data from Protocol OM-EPA-003 (EVOLVE) do not show proarrhythmic liability for EPANOVA.

## BACKGROUND

EPANOVA (omefas) capsules are being developed by the Sponsor for the treatment of lipid disorders. Epanova® (omefas) capsules contain 1000 mg of marine-derived fatty acids which are primarily a concentrate of 55% eicosapentaenoic acid and 20% docosahexaenoic acid in their free fatty acid forms.

A TQT waiver was granted for EPANOVA. DMEP is requesting QT-IRT to review ECG data from the EVOLVE trial (Protocol OM-EPA-003) and provide comments on sponsor's findings.

ECG data were reviewed in a previous consult (July 19 2012) and comments provided were the following:

*Protocol OM-EPA-003; EVOLVE is a prospective, double-blind, randomized, parallel 4-arm study assessing 332 subjects under 12 weeks of treatment. Twelve-lead electrocardiograms (ECG) are collected at baseline (Visit 3-week -1) and at steady-state (Visit 8/ET; week 12 on treatment or early termination). The Visit 8 ECG was used to compare to the baseline in each treatment group: placebo, omepras 2, 3 and 4 g/day. ECGs were originally read by the Investigator at each clinical site. Paper ECGs were retrospectively sent to a central laboratory for a blinded high-resolution reading by a central cardiologist blinded to the study treatment. Mean changes from baseline for QTcF, PR and QRS duration placebo-corrected were not clinically meaningful for any of the dose groups (2, 3 and 4 g/d). No subject had a QTcF > 500 ms or a post-baseline increase > 60 ms. No subject had an increase incidence in morphological ECG changes compared to placebo. The mean change from baseline for heart rate placebo-corrected was not clinically meaningful.*

Thank you for requesting our input into the development of this product under NDA 205060. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cdcrpqt@fda.hhs.gov](mailto:cdcrpqt@fda.hhs.gov)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MONICA L FISZMAN  
12/15/2013

NORMAN L STOCKBRIDGE  
12/16/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 205060 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Epanova (proposed) Established/Proper Name: omefas (proposed) Dosage Form: Capsule Strengths: 1 gram		
Applicant: Omthera Pharmaceuticals Agent for Applicant (if applicable): N/A		
Date of Application: 7/3/2013 Date of Receipt: 7/5/2013 Date clock started after UN: N/A		
PDUFA Goal Date: 5/5/2014	Action Goal Date (if different):	
Filing Date: 9/3/2013	Date of Filing Meeting: 8/29/2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) TBD		
Proposed indication: adjunct to diet to reduce triglyceride (TG), <span style="background-color: #cccccc; color: #000000;">(b) (4)</span> levels in adult patients with severe $\geq 500$ mg/dL hypertriglyceridemia.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): IND 107616				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p>X Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p>X Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b> (NDAs/NDA Efficacy Supplements only)</p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1488 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p>X</p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDA</i> s/ <i>NDA efficacy supplements only</i> )  <b>If yes</b> , # years requested: 5  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDA</i> s <i>only</i> )?	<input type="checkbox"/>	X	<input type="checkbox"/>	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 ( <i>NDA</i> s/ <i>NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLA</i> s/ <i>BLA efficacy supplements</i> ) including:	X	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input type="checkbox"/>	X		Contains omega-3-fatty acids EPA, DHA and DPA. EPA and DHA are found in esterified form in LOVAZA, and VASCEPA, both approved drugs

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL	X	<input type="checkbox"/>		

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<b>X Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 6/2/2010	X	<input type="checkbox"/>		Minutes issued 7/7/2010
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 11/14/2012	X	<input type="checkbox"/>		Minutes issued 12/18/2012
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 10/22/2010	X	<input type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** August 29, 2013

**BLA/NDA/Supp #:** NDA 205060

**PROPRIETARY NAME:** Epanova

**ESTABLISHED/PROPER NAME:** omefas

**DOSAGE FORM/STRENGTH:** Capsules, 1 gram

**APPLICANT:** Omthera

**PROPOSED INDICATION:** adjunct to diet to reduce triglyceride (TG), [REDACTED] (b) (4) levels in adult patients with severe  $\geq 500$  mg/dL) hypertriglyceridemia.

**BACKGROUND:** IND 107616 was submitted March 25, 2010, and included an End-of-Phase 2 (EOP2) meeting request to discuss the applicant's plan to develop this compound as an adjunct to diet for the treatment of severe hypertriglyceridemia ( $>500$  mg/dL). According to the sponsor, Epanova is 20% DHA and 55% EPA (extracted from fish oil) in their free fatty acid forms and has the potential advantage of greater bioavailability than existing omega-3-fatty acid alternatives.

Epanova was previously investigated in the Division of Gastrointestinal and Inborn Errors Products for the treatment of Crohn's Disease (IND [REDACTED] (b) (4) (EPIC studies). The sponsor of that application was Tillots Pharma AG, and ownership of the application was transferred to Omthera on December 8, 2009.

An EOP2 meeting was held on June 2, 2010, and, at that meeting, the firm was notified that an indication involving an add-on to statin therapy would require a CV outcomes trial be underway with approximately 50% of the patients enrolled at the time of NDA/supplement submission.

During drug development, the following clinical protocols were reviewed under the Special Protocol Assessment program:

1. OM-EPA-003 (later called EVOLVE): *Efficacy and Safety of Epanova® in Severe Hypertriglyceridemia*. An "agreement" letter issued October 22, 2010.
2. OM-EPA-004 (later called ESPRIT): *A 6-Week, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Add-on Epanova to Statin Therapy in High-Risk Subjects with Persistent Hypertriglyceridemia*. An "agreement" letter issued May 31, 2011.
3. OM-EPA-005 (STRENGTH): *A Phase III, Double-Blind, Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia*. An "agreement" letter issued March 16, 2012.

On April 25, 2012, the applicant requested agency concurrence on the proposal to, in lieu of conducting a thorough QTc study, assess ECGs recorded pre-dose and during periods of trough levels after dosing with dosing with Epanova for multiple days in the EVOLVE study. This proposal was found acceptable on October 3, 2012.

The firm submitted this 505(b)(1) application for the treatment of severe hypertriglyceridemia, based on the EVOLVE study.

Following approval, the applicant is proposing to pursue an additional indication based on the ESPRIT study: (b) (4)

. The initial NDA application will include the results from ESPRIT to further support the safety and efficacy of Epanova, however, the supplement for that indication will not be submitted until there is approximately 50% enrollment in the CV outcomes trial (STRENGTH).

(b) (4) (b) (4)

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kati Johnson	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Eric Colman		N
Clinical	Reviewer:	Iffat Chowdhury/Efficacy Giovanni Cizza/Safety	Y
	TL:	James P. Smith	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sury Sista	Y
	TL:	Immo Zadezensky	N
Biostatistics	Reviewer:	Cynthia Liu	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Parvaneh Espandiari	N
	TL:	Karen Davis Bruno	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Martin Haber/CMC Houda Mahayni/Biopharm	Y Y
	TL:	Su Tran Angelica Dorantes	Y Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Bryan Riley	N
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Steve Hertz	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Cynthia LaCivita	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Mary Parks, Acting Division Director		Y
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<p>X YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<p>X Not Applicable</p>
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Requesting a rationale for assuming the applicability of foreign data in the application to the US population.</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p>X Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul>	<p>X YES</p> <p><input type="checkbox"/> NO</p>

<p><b>If no, explain:</b></p>	
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Requesting the bioanalytical report for Study SPC-275-4 (A Randomized, Placebo-Controlled Study of the Safety, Tolerability and PK of Multiple Ascending Oral Doses of a Highly Concentrated n-3 Polyunsaturated Fatty Acids (PUFAs) Oil Derived from Fish Oil in Healthy Subjects)</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> CMC requested that the sponsor provide a copy of their application for a USAN name and advise us of the progress of that application. Biopharm has several requests to be included in the letter</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?  <b>If no</b>, was a complete EA submitted?  <b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b> A review of proposed microbial controls was archived 7/19/2013.</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> EER requested 7/15/2013</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority: TBD</b></p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 11/20/2013</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  X Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  X Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	<p>Send review issues/no review issues by day 74</p>
<input type="checkbox"/>	<p>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</p>
<input type="checkbox"/>	<p>Update the PDUFA V DARRTS page (for NME NDAs in the Program)</p>
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:  <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	<p>Other</p>

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATI JOHNSON  
09/12/2013