CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210589Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval.

NDA 210589
Review # 1
Omegaven® (fish oil triglycerides) injectable emulsion

Drug Name/Dosage Form	Omegaven (fish oil triglycerides) Injectable Emulsion
Strength	5g/50mL and 10g/100mL (0.1g/mL)
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi USA, LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
1	07/14/2017	Pre-NDA submission - Multiple Categories
2	09/25/2017	Original NDA Submission - Multiple Categories
3	12/01/2017	Clinical Overview and Clinical Study Reports
4	12/27/2017	Response to Clinical Information Request
5	01/12/2018	Cross Reference to INDs - Clinical
6	01/16/2018	Response to Clinical Information Request
7	01/24/2018	Administrative Information - Multiple Categories
8	01/29/2018	Respond to Quality Information Request - Drug Substance
9	01/30/2018	Response to Clinical Information Request
10	02/05/2018	Quality Amendment - Drug Substance and Drug Product
11	02/06/2018	Response to Clinical Information Request
12	02/08/2018	Response to Clinical Information Request
13	02/15/2018	Respond to Quality Information Request - Drug Substance
14	02/20/2018	Amendment - Labeling
15	02/22/2018	Response to Clinical Information Request
16	03/01/2018	Respond to Quality Information Request - Microbiology
17	03/15/2018	Respond to Quality Information Request - Manufacturing Process
18	03/19/2018	Response to Clinical Information Request
19	03/30/2018	Response to Clinical Information Request
20	04/16/2018	Amendment - Multiple Categories - Clinical and Drug substance
21	04/18/2018	Amendment - Multiple Categories - Clinical and Nonclinical
22	04/20/2018	Response to Information Request - Biometrics
23	04/26/2018	Response to Clinical Information Request
24	04/27/2018	Respond to Quality Information Request - Microbiology
25	05/19/2018	Response to Quality Information Request - Drug Substance and Drug Product

26	05/11/2018	Amendment - Multiple Categories - Clinical and Labeling
27	05/31/2018	Quality Amendment - Drug Substance
28	06/01/2018	Labeling Amendment - Package Insert
29	06/07/2018	Response to Clinical Information Request
30	06/14/2018	Response to Quality Information Request – Microbiology
31	06/21/2018	Labeling Amendment - Package Insert
32	06/25/2018	Response to Clinical Information Request
33	06/26/2018	Clinical – PMR and PMC
34	06/28/2018	Respond to Quality Information Request – Nonclinical and Drug Product
35	07/02/2018	Labeling Amendment – Immediate Container and Carton Labels
36	07/06/2018	Labeling Amendment - Package Insert

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber, Ph.D.	Donna Christner, Ph.D.
Drug Product	Hamid Shafiei, Ph.D.	Moo-Jhong Rhee, Ph.D.
Labeling	Hamid Shafiei, Ph.D.	Moo-Jhong Rhee, Ph.D.
Process	Yuesheng Ye	N. Chidambaram, Ph.D.
Microbiology	Jennifer Patro, Ph.D.	Erika Pfeiler, Ph.D.
Facility	B.J. Ryan	Vidya Pai
Biopharmaceutics	Vincent Duan, Ph.D.	Tien-Mien Chen, Ph.D.
RBPM	Oumou Barry, MHA, MT, ASCP	N/A
Application Technical Lead	Hamid Shafiei, Ph.D.	N/A
Laboratory (OTR)	N/A	N/A
Environmental Analysis (EA)	Raanan Bloom, Ph.D.	Scott Furness, Ph.D.

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)	(b) (4) Rubber Stoppers	N/A		
	Type III		(b) (4) Rubber Stoppers	N/A		
	Type III		(b) (4) Glass Bottles	N/A		
	Type III		(b) (4) Glass Bottles	N/A		

quate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	N/A	N/A

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance and the drug product.

All labels/labeling issues have been satisfactorily resolved.

The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.

Therefore, from the OPQ perspective, this NDA is recommended for **APPROVAL** with the drug product expiration dating period of **18 months**.

II. Summary of Quality Assessments

A. Product Overview

Fresenius Kabi USA, LLC has submitted this (505)(b)(1) new drug application for Omegaven® (fish oil triglycerides) Injectable Emulsion, 5g/50mL and 10g/100mL (0.1g/mL) intended for intravenous infusion as a supply of calories in patients with parenteral nutrition-associated cholestasis. Omegaven has been approved in Europe and other counties since 1998 for the treatment of adult patients. Omegaven has also been used in the United States under single patient compassionate use as well as expanded access INDs as an alternative to soybean oil for the supply of fat calories in infants and pediatric patients with parenteral nutrition-associated liver disease (PNALD) and parenteral nutrition-associated cholestasis (PNAC).

The fish oil triglycerides used as the active ingredient of Omegaven® is produced from (b) (4) fish oil and is rich in ω3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as the two major components. In addition, this (b) (4) fish oil contains ω 6 and ω 9 fatty acids as the other natural components.

Fish oil is complex mixture and the composition of the components of this (b) (4) fish oil differs from dietary supplement monographed the USP/NF. Therefore, this active ingredient of Omegaven® has been granted a new molecular entity (NME) designation with the Agency recommended established name of "fish oil triglycerides".

Omegaven is an oil-in-water emulsion and contains dl-alpha-tocopherol, glycerol, purified egg phospholipids, sodium oleate, sodium hydroxide (minor amount if needed, for pH adjustment), and water for injection as the inactive ingredients. Omegaven can be used alone or as a component of total parenteral nutrition (TPN) combined with admixes containing other components of TPN such as amino acids, carbohydrates, vitamins, minerals, and electrolytes prior to intravenous infusion.

Omegaven (fish oil triglycerides) Injectable Emulsion is a sterile, nonpyrogenic, homogenous, white emulsion for intravenous infusion and will be marketed in the United States as 5g/50mL and 10g/100mL (0.1g/mL) supplied in USP (b) (4) glass bottles with (b) (4) rubber stopper closures oversealed with aluminum-plastic flip caps.

Proposed Indication(s) including Intended Patient Population	**As a supply of calories in patients with parenteral nutrition-associated cholestasis**
Duration of Treatment	**Intravenous infusion into a central or peripheral vein over a period of 8 to 24 hours. Duration of treatment varies based on patient's need**
Maximum Daily Dose	**The recommended dose and the maximum dose in pediatric patients is 1g/kg/day**
Alternative Methods of Administration	**Not applicable**

B. Quality Assessment Overview

Drug Substance:

The active ingredient of Omegaven is triglycerides produced from (b) (4) fish oil. It is a pale-yellow oil. It is insoluble in water, slightly soluble in ethanol, and very soluble in acetone and heptane. Fish oil consists solely of long chain fatty acid triglycerides. (b) (4) fish oil triglycerides are enriched in omega-3 acids and include about (b) (4)% eicosapentaenoic acid (EPA) and about (b) (4)% docosahexaenoic acid (DHA). It also contains about (b) (4)% myristic acid, (b) (4)% palmitic acid, (b) (4)% palmitoleic acid, and (b) (4)% oleic acid as well as many other unspecified fatty acids. This active ingredient contains a total of about (b) (4)% omega-3 fatty acids including linoleic acid, arachidonic acid and (b) (4), and a total of about (b) (4)% omega-6 fatty acids. (b) (4) d-l-α-tocopherol, (vitamin E) is added to this drug substance as the antioxidant ((b) (4)%). Since the composition of fatty acid components of (b) (4) fish oil used as the active ingredient of Omegaven® is different from previously approved fish oil containing drug products and/or the fish oil described in the USP monograph, it has been granted an NME status.

(b) (4)

The drug substance is tested and release according to a specification that includes testing and acceptance criteria for the identity, absorbance, stearin, peroxide value, anisidine value, total oxidation value, acid value, unsaponifiable matter, specified fatty acid contents, d-l-α-tocopherol content, residual solvents, elemental impurities, environmental contaminant ((b) (4)) microbial bioburden and bacterial endotoxin.

The Drug Substance Reviewer, Dr. Martin Haber has found the CMC information provided in the drug substance section of this application as sufficient to assure the identity, strength, purity, and quality of the active ingredient. Dr. Haber has recommended the **approval** of this new drug application from the drug substance perspective.

Drug Product:

Omegaven (fish oil triglycerides) Injectable Emulsion for intravenous infusion is a sterile, nonpyrogenic, homogenous, oil-in water, white emulsion supplied as 5g/50mL and 10g/100mL in USP (b) (4) glass bottles closed with (b) (4) rubber stoppers oversealed with aluminum-plastic flip caps. Omegaven is intended as a supply of calories for patients with PNAC. Omegaven Injectable Emulsion has been approved for marketing in Europe and other countries since 1998 for use in the treatment of adult patients.

Omegaven contains triglycerides produced from highly refined fish oil as the active ingredient and dl-alpha-tocopherol, glycerol, purified egg phospholipids, sodium oleate, sodium hydroxide (minor amount if needed, for pH adjustment), and water for injection as the inactive ingredients. The total energy content of Omegaven Injectable emulsion is 112kcal/100mL (1.12kcal/mL).

The pharmaceutical/formulation development studies for this drug product were conducted based on the desired quality target product profile (QTPP) for a sterile, nonpyrogenic, homogeneous, stable, injectable emulsion intended for intravenous infusion as a supply of calories to be administered alone or to be combined with the available standard admixes as a component of the total parenteral nutrition (TPN) prior to administration to patients with parenteral nutrition-associated cholestasis (PNAC).

The development of the drug product with the desired QTPP that complies with ICH guidelines and the USP compendial requirements was achieved by focusing on three major considerations. 1) formulation of a stable, sterile, nonpyrogenic, and homogeneous injectable emulsion composed of (b) (4) fish oil and compendial excipients, 2) formulation should be compatible with standard admixes used in TPN therapy, 3) selection of compatible primary container closures that (b) (4) are capable of properly protecting the drug product from external environment and maintaining the drug product stability and sterility throughout its intended shelf-life of 18 months.

Although d-l-α-tocopherol, a known antioxidant was added to the drug substance to (b) (4)

The compatibility of the selected 50-mL and 100-mL (b) (4) glass bottles and (b) (4) rubber stopper closures that come in contact with the drug product emulsion was established through extractable/leachable and migration studies. The ability of the container closure systems, bottles with rubber stopper closures oversealed with the aluminum-plastic flip caps, for maintaining the drug product stability and sterility during the shelf-life storage was confirmed through accelerated and long-term stability studies.

Finally, compatibility of Omegaven (fish oil triglycerides) formulation with admixes and additives commonly used in the preparation of TPN mixtures was confirmed by 48-hour in-used stability studies of several combinations of Omegaven with common TPN admixes and additives.

In summary, although this drug product has been approved in Europe and other countries since 1998, the applicant has provided CMC information that includes data from product development studies that supports the proposed composition of the final drug product, drug product specifications consistent with ICH Q3B that is considered adequate for the control of the physical and chemical quality attributes of the drug product, data from compatibility studies of the drug product with the primary container closure systems and common TPN admixes, accelerated and long-term stability data from exhibit batches of drug product manufactured at the commercial scale at the proposed commercial manufacturing site that supports of the proposed expiration dating period of 18 months.

The Drug Product Reviewer/ATL, Dr. Hamid Shafiei has concluded that the CMC information provided in this application is sufficient to assure the identity, strength, purity, and quality of the drug product at release and throughout its proposed shelf-life. Dr. Shafiei has recommended the **approval** of this new drug application with **expiration dating period of 18 months**.

Process

The drug product manufacturing process steps for Omegaven (fish oil triglycerides) Injectable Emulsion, 5g/50mL and 10g/100mL includes (b) (4)

The information regarding the drug product manufacturing process, control of the critical manufacturing steps, and in-process controls submitted in this application has been reviewed by the OPF Process Reviewer, Dr. Yuesheng Ye. Dr. Ye has concluded

that the proposed manufacturing process and process controls for Omegaven® are adequate.

Biopharm

The review of the Biopharm Section of this application has been performed by the OPQ Biopharm Reviewer Dr. Vincent Duan. Dr. Duan has concluded that since this drug product is an injectable emulsion for intravenous infusion, no biopharm evaluation is needed. Therefore, Dr. Duan has recommended the **approval** of this application from the Biopharm standpoint.

Microbiology

In addition to the review of the proposed manufacturing process by Dr. Ye, the review of the adequacy of the proposed drug product (b) (4) sterilization process validation and controls, validity of each test method used in the determination the drug product package integrity, sterility, and bacterial endotoxins, and the corresponding acceptance criteria in the drug product specification has been performed by the OPF Microbiology Reviewer, Dr. Jennifer Patro. In her review, Dr. Patro has concluded that the proposed sterilization process and process controls for Omegaven are adequate. She has further evaluated and accepted test methods used in the determination of sterility, bacterial endotoxins, and packaged integrity as valid. Dr. Patro has also found the proposed acceptance criteria for sterility and bacterial endotoxins in the drug product specification to be adequate. Dr. Patro has recommended the **approval** of the application from the Microbiology perspective.

Facilities

Facilities involved in this application has been reviewed by the OPF Facilities Reviewer, Mr. B.J Ryan. Mr. Ryan has made the overall conclusion that all facilities involved in this application are **acceptable**. Mr. Ryan also stated that the single outside facility identified by the applicant that will perform contract laboratory operation in support of the drug product manufacturing and release operation within compliance standards and can perform the functions and responsibilities outlined in the application. No post-approval inspection except that a routine surveillance has been recommended by Mr. Ryan.

Environmental Assessment

Since the active ingredient of this drug product, (b) (4) fish oil, is an animal-derived substance, the review of the applicant's claim for the categorical exclusion from the preparation of environmental assessment according to 21CFR 25.31(c) has been performed by the OPQ Environmental Assessment (EA) Reviewer, Dr. Raanan A. Bloom. Dr. Bloom has found the applicant's claim for the categorical exclusion under 21CFR 25.31(c) valid and that the available information supports the statement of "no extraordinary circumstances". Dr. Bloom has recommended that the categorical exclusion from the preparation of environmental assessment for this application can be **granted**.

C. Special Product Quality Labeling Recommendations (NDA only)

Not applicable

D. Final Risk Assessment (see Attachment)

Omegaven has been approved and marketed in Europe and other countries since 1998. Based on more than 20 years of drug product knowledge and manufacturing experience, and the fact that no significant CMC changes to drug substance or drug product have been made since its original approval, risk assessment for this drug product was deemed unnecessary.

E. List of Deficiencies:

None

Application Technical Lead Name and Date:

Hamid. R. Shafiei, Ph.D.
Reviewer, Branch V/DNDP II/ONDP/OPQ

124 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ENVIRONMENTAL

R Regional Information

Background

Application: NDA 210509
API: Omegaven (fish oil injectable emulsion), for intravenous use
Indication: Omegaven is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis

Omegaven fish oil is a triglyceride mixture consisting of esters of long-chain saturated fatty acids and unsaturated fatty acids.

The source of Omegaven oil is [redacted] (b) (4) .

The applicant has submitted a claim of categorical exclusion under 21CFR 25.31(c) and a statement of "no extraordinary circumstances." The applicant provided additional information on February 5, 208 in response to a January 24, 2018, IR.

Based on the characteristics of Omegaven, the application meets the criteria for the cited categorical exclusion. This review then evaluates the "extraordinary circumstances" statement to determine if approval could adversely affect a species or the critical habitat of a species determined under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species (CITES) of Wild Flora and Fauna to be endangered or threatened or wild flora or fauna that are entitled to special protection under some other Federal law. (21 CFR 25.21b).

Environmental Review

In the January 24, 2018 IR, the applicant was requested to provide information on whether approval could adversely affect a species or the critical habitat of a species determined under ESA or CITES to be endangered or threatened or wild flora or fauna that are entitled to special protection under some other Federal law. The following information was provided:

(1) **Biological identification**: [redacted] (b) (4)
(2) **Specimens are used**: [redacted] (b) (4)
(3) **Geographic region where the biomass is obtained**: [redacted] (b) (4)
(4) **Species information**:

- *Is the species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened:* ***NO***

- *Is the species entitled to special protection under some other Federal law or international treaty to which the United States is a party:* ***NO***

- *Is the species the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or CITES:* ***NO***
- *Is the species the critical habitat of a species entitled to special protection under some other Federal law or international treaty to which the United States is a party:* ***NO***

In addition, information was requested on required permits or other authorizations for (b) (4). The following information was provided:

"As the starting material (b) (4) no special permits or authorizations are required for the harvesting. The (b) (4) required for the manufacture of the starting material, (b) (4) is obtained by the supplier from (b) (4). These fisheries are certified by IFFO (International Fishmeal and Fish Oil Organization) and controlled by several official organizations such as survey of fish populations, regulation of fishing quotas, regulations of seasons of fishery, and catch limits per vessel."

The provided information indicates that the fish from which Omegaven is derived are not endangered or threatened, not listed on CITES or ESA and controls are in place to regulate fishing quotas in efforts to sustain fish populations. A Full EA is not required.

Reviewer's Assessment: ***Adequate***

The applicant has submitted a claim of categorical exclusion under 21CFR 25.31(c) and a statement of "no extraordinary circumstances" for Omegaven (fish oil injectable emulsion), for intravenous use. The application meets the criteria for the cited categorical exclusion. Available information supports a statement of "no extraordinary circumstances." The fish source of Omegaven is not a CITES or ESA listed species. The fisheries are IFFO certified and fishing quotas are regulated. Significant impact to the environment due to approval of this application is not anticipated.

The applicant's claim of claim of categorical exclusion under 21 CFR 25.31(c) and statement of no extraordinary circumstance is acceptable.

Primary Environmental Reviewer: Raanan A. Bloom, Ph.D.

Secondary Reviewer: Scott Furness, Ph.D.

Raanan Bloom

Digitally signed by Raanan Bloom
Date: 4/26/2018 03:24:29PM
GUID: 508da72a0002a6d1071f3297897e4f1f

Michael Furness

Digitally signed by Michael Furness
Date: 4/27/2018 07:41:53AM
GUID: 502e8c7600003dd8331cf6eebf43697a

LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

These highlights do not include all the information needed to use OMEGAVEN safely and effectively. See full prescribing information for OMEGAVEN.

2) OMEGAVEN (fish oil triglycerides) injectable emulsion, for intravenous use
Initial U.S. Approval: 2018

3) DOSAGE FORMS AND STRENGTHS

Injectable Emulsion: 5 g/50 mL and 10 g/100 mL (0.1 g/mL) in a single-dose bottle. (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	OMEGAVEN (fish oil triglycerides)	Provided. **Satisfactory**
Dosage form, route of administration	Injectable Emulsion, for intravenous use	Provided. **Satisfactory**
Controlled drug substance symbol (if applicable)	Not Applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))	Injectable Emulsion: 5 g/50 mL and 10 g/100 mL (0.1 g/mL) in a single-dose bottle	Provided. **Satisfactory**
Whether the drug product is scored	Not applicable.	Not applicable.

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

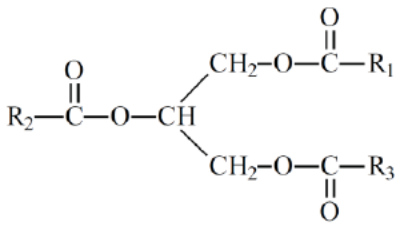
Injectable Emulsion: 5 g/50 mL and 10 g/100 mL (0.1 g/mL) sterile, white, homogenous emulsion in a 50-mL and 100-mL single-dose bottles.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Injectable Emulsion: 5 g/50 mL and 10 g/100 mL (0.1 g/mL) sterile, white, homogenous emulsion in a 50-mL and 100-mL single-dose bottles.	Provided. **Satisfactory**
Strengths: in metric system	5 g/50 mL 10 g/100 mL	Provided. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable	Not applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	sterile, white, homogenous emulsion in a 50-mL and 100-mL single-dose bottles.	Provided. **Satisfactory**

2) #11: Description

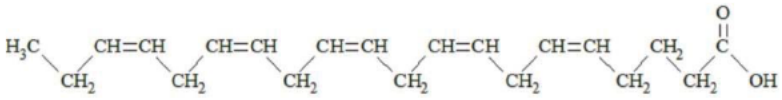
Omegaven (fish oil triglycerides) is a sterile, nonpyrogenic, white, homogenous emulsion for intravenous infusion as a supply of calories in patients with PNAC. Each mL of Omegaven contains 0.1 g of fish oil, 0.012 g egg phospholipids, 0.025 g glycerin, 0.15 to 0.3 mg dl-alpha-tocopherol, 0.3 mg sodium oleate, water for injection, and sodium hydroxide for pH adjustment (pH 6 to 9). The phosphate content is 0.015 mmol.

The fish oil included in Omegaven is a triglyceride mixture consisting of esters of long-chain saturated fatty acids and unsaturated fatty acids with the following structure:

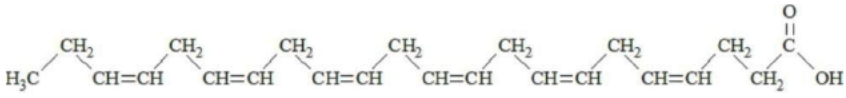


where R_1CO-, R_2CO-, and R_3CO- are long chain acyl groups. Because triglycerides often contain different long chain fatty acids at each position, possible structures can have molecular weights ranging from 700 to 1000 g/mol. The main fatty acid components of the fish oil in Omegaven are EPA (13% to 26%) and DHA (14% to 27%). The fish oil also contains palmitic acid (4% to 12%), oleic acid (4% to 11%), palmitoleic acid (4% to 10%), myristic acid (2% to 7%), and arachidonic acid (0.2% to 2.0%). Additionally, the mean contents of linoleic acid and alpha linolenic acid are 1.5(b) (4)% and 1.1%, respectively. The fish oil component has a total omega-3 fatty acid content of 40% to 54%. The empirical formula, molecular weight, and chemical structure of the main fatty acid components are:

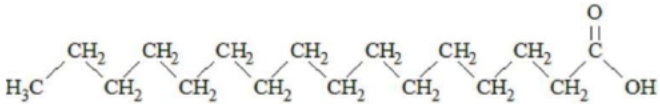
EPA
$C_{20}H_{30}O_2$
302.45



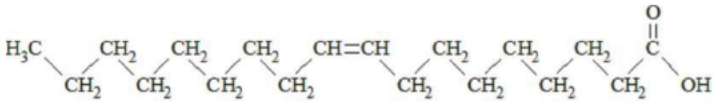
DHA
$C_{22}H_{32}O_2$
328.49



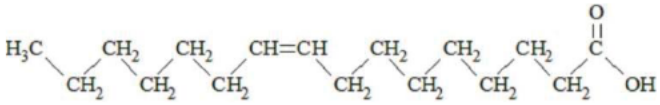
Palmitic acid
$C_{16}H_{32}O_2$
256.43



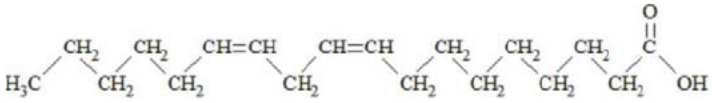
Oleic acid
$C_{18}H_{34}O_2$
282.47



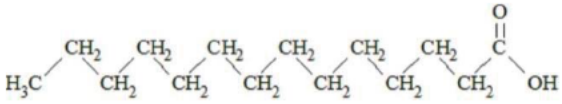
Palmitoleic acid
$C_{16}H_{30}O_2$
254.41



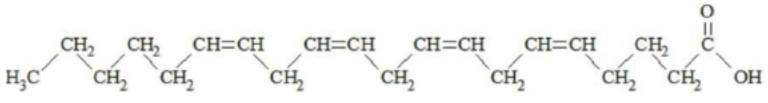
Linoleic acid
$C_{18}H_{32}O_2$
280.45



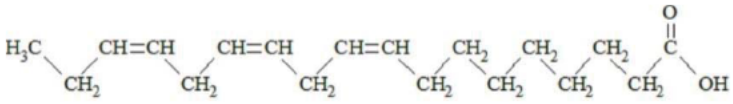
Myristic acid
$C_{14}H_{28}O_2$
228.38



Arachidonic acid
$C_{20}H_{32}O_2$
304.47



Alpha-linolenic acid
$C_{18}H_{30}O_2$
278.44



Omegaven 5 mg/(b) (4) 50 mL contains 5 grams of fish oil and 0.6 g egg phospholipids, 1.25 g glycerin, 7.5 to 15 mg dl-alpha-tocopherol, 0.015 g sodium oleate, water for injection, and sodium hydroxide for pH adjustment (pH 6 to 9) packaged in a single-dose 50-mL glass bottle enclosed with a rubber stopper. The phosphate content of the drug product is 0.75 mmol. The mean content of the two major fatty acid components in 50 mL are 1.0 g EPA (range: 0.6 to 1.5 g) and 0.96 g DHA (range: 0.7 to 1.7 g). Additionally, the mean content of linoleic acid, alpha-linolenic acid, and arachidonic acid per 50 mL are 0.16 g, 0.07 g, and 0.13 g; respectively.

Omegaven 10 mg/100 mL contains 10 grams of fish oil and 1.2 g egg phospholipids, 2.5 g glycerin, 15 to 30 mg dl-alpha-tocopherol, 0.03 g sodium oleate, water for injection, and sodium hydroxide for pH adjustment (pH 6 to 9) packaged in a single-dose 100-mL glass bottle enclosed with rubber stopper. The phosphate content of the drug product is 1.5 mmol. The mean content of the two major fatty acid components in 100 mL are 2.0 g EPA (range: 1.2 to 3.0 g) and 1.9 g DHA (range: 1.3 to 3.3 g). Additionally, the mean content of linoleic acid, alpha-linolenic acid, and arachidonic acid per 100 mL are 0.31g, 0.13 g, and 0.25 g; respectively.

The total energy content of Omegaven is 112 kcal/100 mL (1.12 kcal/mL), including lipids, phospholipids, and glycerol.

Omegaven has an osmolality of approximately 342 mOsm/kg water (which represents an osmolarity of 273 mOsm/L).

Omegaven contains no more than 25 mcg/L of aluminum.

The stopper used as the bottle closure is not made with natural rubber latex, PVC, or DEHP.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	Omegaven (fish oil triglycerides)	Provided. **Satisfactory**
Dosage form and route of administration	emulsion for intravenous infusion	Provided. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable	Not applicable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Provided.	Provided. **Satisfactory**
Statement of being sterile (if applicable)	a sterile, nonpyrogenic, white, homogenous emulsion for intravenous infusion	Provided. **Satisfactory**
Pharmacological/ therapeutic class	as a supply of calories in patients with PNAC	Provided. **Satisfactory**
Chemical name, structural formula, molecular weight	Names, empirical formulas, molecular masses, and structures for main fatty acid components of the active ingredient has been provided in text above and due to the size limitations are not copied here.	Provided. **Satisfactory**
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa or pH)	The total energy content of Omegaven is 112 kcal/100 mL (1.12 kcal/mL), including lipids, phospholipids, and glycerol. Omegaven has an osmolality of approximately 342 mOsm/kg water (which represents an osmolarity of 273 mOsm/L). Omegaven contains no more than 25 mcg/L of aluminum. The stopper used as the bottle closure is not made with natural rubber latex, PVC, or DEHP.	Provided. **Satisfactory**

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

Omegaven (fish oil triglycerides) injectable emulsion, 5 g/50 mL and 10 g/100 mL (0.1 g/mL) is a white, homogenous, sterile emulsion supplied as follows:

50 mL glass bottle	NDC 63323-205-21
Carton of 10 x 50 mL	NDC 63323-205-50

100 mL bottle	NDC 63323-205-31
Carton of 10 x 100 mL	NDC 63323-205-00

Store below 25°C (77°F). Avoid excessive heat. Do not freeze. If accidentally frozen, discard product.

Once the bottle is connected to the infusion set, use Omegaven immediately. Complete infusion within 12 hours when using a Y-connector [see Dosage and Administration (2.1)].

Infuse admixtures containing Omegaven immediately. If not used immediately, admixtures can be stored for up to 6 hours at room temperature or up to 24 hours under refrigeration. Complete the infusion within 24 hours after removal from storage [see Dosage and Administration (2.2)].

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	Omegaven (fish oil triglycerides) injectable emulsion, 5 g/50 mL and 10 g/100 mL (0.1 g/mL)	Provided **Satisfactory**
Available units (e.g., bottles of 100 tablets)	50 mL glass bottle Carton of 10 x 50 mL 100 mL bottle Carton of 10 x 100 mL	Provided. **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	a white homogenous emulsion. NDC number are provided.	Provided. **Satisfactory**
Special handling (e.g., protect from light)	Avoid excessive heat. Do not freeze. If accidentally frozen, discard product.	Provided. **Satisfactory**
Storage conditions	Store below 25°C (77°F)	Provided. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by: FRESENIUS KABI Graz, Austria	Provided. **Satisfactory**

II. Labels

1. IMMEDIATE CONTAINER

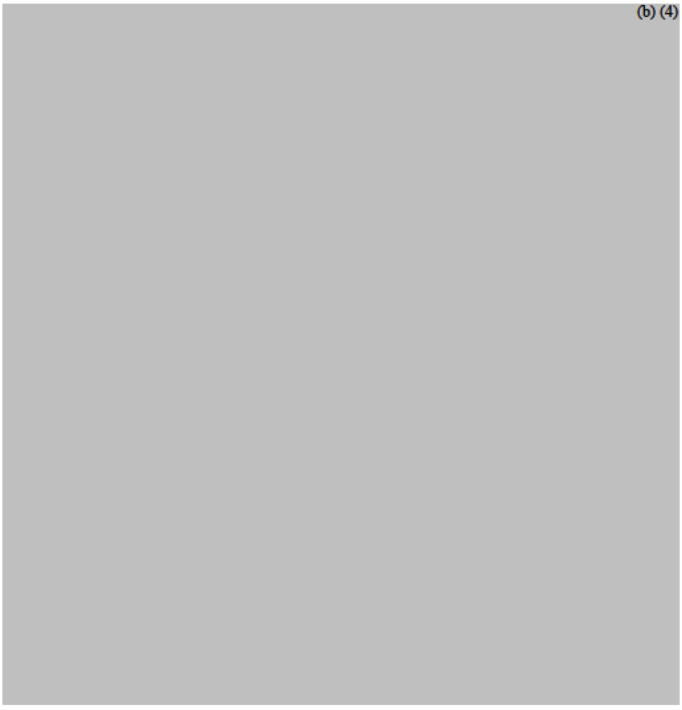
5g/50mL Container Label

10g/100mL Container Label

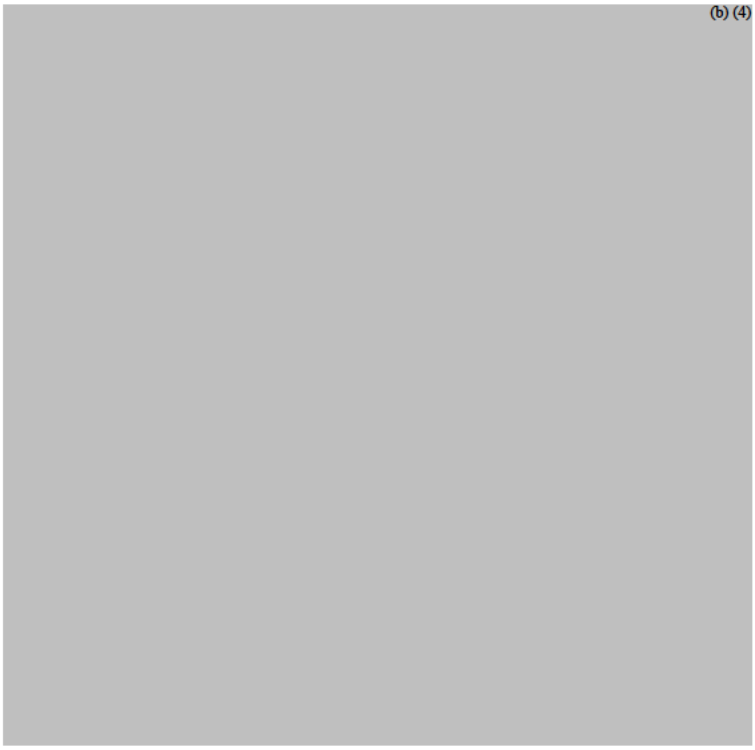
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Omegaven® (Fish Oil) Injectable emulsion,	Displayed. **Satisfactory**
Dosage strength	5 grams per 50 mL 10 grams per 100 mL	Provided. **Satisfactory**
Net contents	50mL 100mL	Provided. **Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed	Displayed. **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	Provided. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Space allocated	Space to display lot number and expiration has been designated. **Satisfactory**
Storage conditions	Store below 25°C. (77°F). Do not freeze.	Provided. **Satisfactory**
Bar code (21CFR 201.25)	Displayed	Not displayed. **Satisfactory**
Name of manufacturer/distributor	Manufactured by: FRESENIUS KABI Graz, Austria	Provided. **Satisfactory**
And others, if space is available	Sterile Once opened, use within 24 hours. Discard (b) (4) unused portion. Use only if the emulsion is homogeneous. Not made with natural rubber latex. Osmolarity: 273 mOsm/L Contains no more than 25 mcg/L of aluminum.	Provided. **Satisfactory**

2. CARTON LABELS

5g/50mL Container Label



10g/100mL Container Label



Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Omegaven® (fish oil triglycerides) Injectable emulsion	Provided. **Satisfactory**
Dosage strength	Injectable Emulsion 5g/50mL 10g/100mL	Provided. **Satisfactory**
Net contents	10 x 50mL 10 x 100mL	Provided **Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed	Provided. **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	Provided. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Space allocated	Space to display lot number and expiration has been designated. **Satisfactory**
Storage conditions	Store below 25°C. (77°F). Do not freeze.	Provided. **Satisfactory**
Bar code (21CFR 201.25)	Displayed	Provided. **Satisfactory**
Name of manufacturer/distributor	Manufactured by: FRESENIUS KABI Austria GmbH A-8055 Graz, Austria	Provided. **Satisfactory**
And others, if space is available	Sterile For intravenous use only. Use only if the emulsion is homogeneous. See prescribing information. Not made with natural rubber latex	Provided **Satisfactory**

III. LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

None

b) Full Prescribing Information

#3: Dosage Forms and Strengths

None

#11: Description

None

#16: How Supplied/Storage and Handling

None

B. Regarding of the Container/Carton Labels:

1) Immediate Container Label:

None

2) Carton Label

None

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

The PI labeling and the immediate container and carton labels are satisfactory from the CMC perspective. Therefore, this application is recommended for approval from the CMC labeling/label perspective.

Primary Labeling Reviewer Name and Date:

Hamid Shafiei, Ph.D.
Reviewer, Branch V
DNDP II/ONDP/OPQ July 10, 2018

Secondary Reviewer:

I agree with Dr. Shafiei's assessment on the labels/labeling and concur with his recommendation for approval of this application from the label/labeling perspective.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP/OPQ July 10, 2018

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 7/11/2018 08:29:59AM
GUID: 507d824300005f344cf8b5e5989f0057

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 7/11/2018 12:37:07PM
GUID: 502d0913000029f9798ca689a802fa55

51 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

IQA Review Guide Reference

Product Background:

NDA: 210589

Drug Product Name / Strength: Omegaven 10%, Fish Oil Injectable Emulsion

Route of Administration: Intravenous infusion

Applicant Name: Fresenius Kabi USA, LLC

Indication(s): A source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)

Review Recommendation:

Review Summary: Adequate
The proposed drug product, Omegaven 10% Fish Oil Injectable Emulsion, containing 10 mg/mL of highly refined fish oil as the active ingredient, is indicated as a source of calories and fatty acids for pediatric patients with parenteral nutrition associated cholestasis (PNAC). The proposed drug product is an injectable emulsion for intravenous (i.v.) infusion; therefore, there is no evaluation for dissolution method. From Biopharmaceutics perspective, NDA 210589 is acceptable and recommended for approval.

List Submissions being reviewed (table): NDA 210589 submitted in June 13, 2017

Concise Description Outstanding Issues Remaining: N/A

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ***{Adequate/Inadequate}N/A***

{Assess method development, method robustness, and criteria; modeling approach}
The proposed drug product is an injectable emulsion for intravenous (i.v.) infusion and there is no bioavailability issue. Although under our current practice, we recommend dissolution testing for some injectable emulsion, especially for nano-suspension; dissolution test is not mandatory and it is recommended case-by-case. Furthermore, the APIs in the proposed drug product including DHA, EPA, palmitic acid, oleic acid,

palmitoleic acid, and myristic acid are frequently seen as diet supplements, and the amounts of these APIs are controlled by respective Assay during routine quality control of the drug product. Overall, after internal discussion, and based on the nature of the proposed drug product and proposed indication, we conclude that dissolution test is not needed for this drug product.

List of Deficiencies:

N/A

Primary Biopharmaceutics Reviewer Name and Date: Vincent (Peng) Duan, Ph.D. 04/02/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Tien-Mien Chen, Ph.D. I concur. 04/16/18

Acting Biopharm. Lead
DB/ONDP/OPQ

Peng Duan

Digitally signed by Peng Duan
Date: 4/16/2018 11:12:47AM
GUID: 54579633000330547a76e69866efb4b3

Tien Mien Chen

Digitally signed by Tien Mien Chen
Date: 4/16/2018 11:15:29AM
GUID: 508da7240002a26723d38018ce005126
Comments: I concur. 04/16/18

MICROBIOLOGY

Product Background:

NDA/ANDA/BLA: NDA 210589

Drug Product Name / Strength: Omegaven 10%

Route of Administration: intravenous infusion

Applicant Name: Fresenius Kabi USA, lLC

Manufacturing Site: Fresenius Kabi Austria GmbH
Hafnerstrasse 36
8055 Graz
Austria

Method of Sterilization: [redacted] (b) (4) **sterilization**

Review Summary: The submission **is recommended** for approval on the basis of product quality microbiology.

List Submissions being reviewed: 9/25/17, 12/01/17, IR response 2/5/18, IR response 3/01/18, IR response 4/27/18, IR response 6/14/18

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: N/A

Remarks Section: This is a rolling submission. The date of the information being reviewed (09/27/17) is the second pre-submission submitted to this NDA. The final submission to the NDA (12/01/17) contains the labeling information.

S Drug Substance

N/A

P.1 Description of the Composition of the Drug Product

- Description of drug product – Omegaven 10%
  This is a white oil-in-water emulsion.
- Drug product composition

(3.2.P.1 Description and Composition of the drug product.pdf)

Ingredient	Function	Quantity/1000 mL

32 have been Withheld in Full as b4 (CCI/TS) immediately following this page

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 6/18/2018 02:59:25PM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

Jennifer Patro

Digitally signed by Jennifer Patro
Date: 6/18/2018 02:58:55PM
GUID: 568e9b140011fe6b07d3ac7b199f2eba

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 7/13/2018 02:19:16PM
GUID: 507d824300005f344cf8b5e5989f0057

Memorandum

To: NDA 210589

From: Donna Christner, Ph.D.
NDAPI Branch Chief

Through: Ali Al-Hakim, Ph.D.
Division Director, NDAPI

Date: 27-Jun-2018

Re: Identification of Established Name

NDA 210589 was submitted on 01-DEC-2017 for a drug product containing "fish oil" as its sole active ingredient. The applicant is seeking approval of this drug product as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis. The Applicant originally submitted the tradename and established name as follows:

Omegaven (fish oil injectable emulsion), for intravenous use

In reviewing the Applicant's submission, the Agency considered whether there is an existing established name for the NDA's drug product or drug substance. While there are a number of fish oil-related monographs in USP, most are for dietary supplements and, in this case, we do not believe that the dietary supplement monographs would be appropriate to describe the (b) (4) fish oil in Omegaven.[1] While Omegaven may meet the *Fish Oil Containing Omega-3 Acids* dietary supplement monograph requirements, the monograph would not provide appropriate controls for the Omegaven drug substance since the standards are different and conformance to the dietary supplement monograph would allow acceptance of a drug substance of lower quality.[2]

The fish oil in Omegaven does not meet the monograph requirements for fish oil-related drug monographs, either. USP currently has a fish oil-related drug substance monograph, *Omega-3-Acid Ethyl Esters*, and a related drug product monograph, *Omega-3-Acid Ethyl Esters Capsules*. Omegaven does not meet these monographs because it has a different fish oil composition, both

[1] Moreover, generally, the Agency does not use dietary supplement monographs as the source for the nonproprietary name for a drug.
[2] For example, the Chemistry, Manufacturing, and Controls (CMC) and quality specifications established for the Omegaven drug substance/drug product under which the Agency would approve NDA 210589 are more stringent than those provided in the dietary supplement monograph.

in specific chemical form (triglycerides vs ethyl esters) and amounts of major fatty acid components. There are 2 other approved fish oil drug products that may have monographs in the future: omega-3 carboxylic acids and icosapent ethyl. Omegaven's composition is different in form and amounts from those products as well. Therefore, the Applicant was advised to submit a request for a USAN name for the drug substance in NDA 210589. The USAN Council declined to designate a name.

SMOFLIPID, an FDA approved drug product marketed by the same Applicant, was titled using the USP drug product monograph for *Lipid Injectable Emulsion*. SMOFLIPID is a fixed-combination product containing four active ingredients: soybean oil, olive oil, medium chain triglycerides, and fish oil. Comparison data submitted by the Applicant and reviewed under NDA 210589 showed that although the fish oil in SMOFLIPID and Omegaven share many major fatty acid components, they differ in the amounts of such components. Discussions were held within the Agency on whether the USP monograph for *Lipid Injectable Emulsion* also recognizes Omegaven. The monograph has the following Description:

> **Lipid Injectable Emulsion**
>
> » Lipid Injectable Emulsion used in total parenteral nutrition is a sterile 10 (0.10 g per mL), 20 (0.20 g per mL), or 30 (0.30 g per mL) percent w/v emulsion in an aqueous vehicle. The aqueous phase contains 0.6 percent to 1.8 percent w/v parenteral Egg Phospholipids in Water for Injection and contains, if necessary, an osmotic agent, such as glycerin in amounts of 1.7 percent to 2.5 percent w/v, or a suitable stabilizer, such as a fatty acid salt. The most frequently used oil present is Soybean Oil, which provides an ample supply of the essential fatty acids: linoleic acid and linolenic acid. Other oils, such as Safflower Oil, Medium-Chain Triglycerides, Olive Oil, Fish Oil, or other suitable oils, can be mixed with Soybean Oil. Hence, Soybean Oil can be the only oil or be part of a mixture of these other oils. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of the total oil(s). It contains no antimicrobial agents. The final products are terminally sterilized.

During internal Agency discussions, the Agency found that the text of the monograph was ambiguous with respect to the presence of soybean oil. Specifically, this ambiguity arises from the text of the monograph that states "[t]he most frequently used oil present is Soybean Oil …" and "Soybean Oil can be the only oil or be part of a mixture of … other oils." (b) (4)

The Agency contacted the USP Monograph staff for USP's insight on the monograph's scope. Although USP recognized that the monograph as written may not provide complete clarity on this matter (and offered to provide clarity on this point in future revisions to the monograph), it stated that at the time of publication, USP was not aware of any marketed products containing a lipid injectable emulsion without soybean oil present. This suggests that the monograph was drafted with soybean oil being a necessary component for the monograph to apply, and supports a determination that Omegaven is likely not an article recognized in the monograph for *Lipid Injectable Emulsion*. Therefore, the Agency does not believe that Omegaven should be titled as

"Lipid Injectable Emulsion" because, if soybean oil is a required component of the applicable monograph, Omegaven would be misbranded because it lacks soybean oil.

Since the Omegaven product is likely not an article recognized in an existing drug monograph and USAN has declined to name it, the Agency considered whether Omegaven or its active ingredient has a common or usual name that would be the established name. The Agency determined that the Applicant's proposal of the established name "fish oil" is not sufficiently specific, and the term "fish oil" is usually used outside the drug context. Without a common or usual name, the Agency determined that a new name would be needed. After review of the data, the following points were taken into consideration:

- This product only has (b) (4)% omega-3 components, so we recommend the name not include "omega-3" as this may suggest that omega-3 fatty acids constitute the major component of the product.
- "Fish Oil" alone is too vague, and may cause confusion, as it is often used in the context of dietary supplements, and not drugs.
- "Fish Oil Triglycerides" describes a product that includes all the various components found in fish oil and greater than 99% of the components are in triglyceride form.

Therefore, the Agency recommends the following name:

Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONNA F CHRISTNER
07/10/2018

ALI H AL HAKIM
07/10/2018