CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207648Orig1s000

PRODUCT QUALITY REVIEW(S)

CMC Review Data Sheet

NDA 207648

Smoflipid (Lipid Injectable Emulsion) 20%, USP

Fresenius Kabi USA, LLC

Tarun Mehta

Review Chemist

Division of New Drug Products II
Branch V
Office of New Drug Products

CMC REVIEW OF NDA 207648
For the Division of Gastroenterology Products (HFD-180)

CMC Review Data Sheet

(Please add page numbers in the review and fix the TOA with correct page numbers)

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CMC Review Data Sheet

1. NDA 207648

2. REVIEW #: 1

3. REVIEW DATE:

4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	September 26, 2014
Amendment 0004	November 21, 2014
Amendment 0009	March 06, 2015
Amendment 0010	March 19, 2015
Amendment 0014	April 21, 2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Fresenius Kabi USA, LLC
Address:	Three Corporate Drive Lake Zurich, IL 60047
Representative:	Lakshmi Rebbapragada, Sr. Regulatory Specialist
Telephone:	(847) 550-2399

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SMOFlipid 20%
b) Non-Proprietary Name: Lipid Injectable Emulsion, USP
c) Code Name/# (ONDP only): None
d) Chem. Type/Submission Priority (ONDP only):

- Chem. Type: 2

- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Parenteral nutrition

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: 20% w/v

13. ROUTE OF ADMINISTRATION: Intravenous infusion

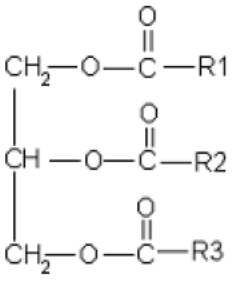
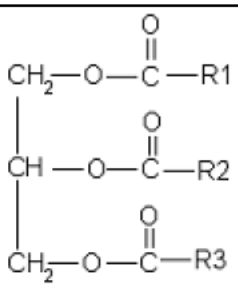
14. Rx/OTC DISPENSED: __√__ Rx ___OTC

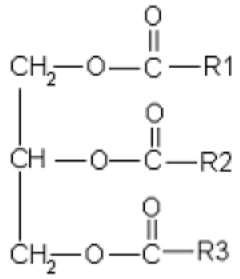
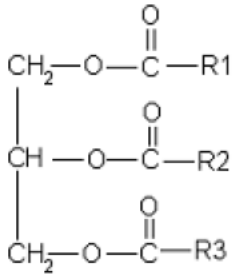
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

√ Not a SPOTS product

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

Chemical names, compendial names, structural formulas, abbreviations for active ingredients:

Chemical Name/ USP name	INN/IUPAC name	Abbreviation	structural formula	MW g/mol	MF
Fish Oil	**Fish Oil**	**None**		**879 g/mol**	**R1, R2 and R3 long chain alkyl group C18, C20,c21 and C22**
Medium Chain Triglycerides **Source: Coconut and Palm Kernels**	**Caprylic and Capric triglycerides**	**None**		**505 g/mol**	**R1, R2 and R3 long chain alkyl group C6,C8,C10, C12 and C14 Major C8 and C10)**

Olive Oil	**None**	**None**			**861 g/mole**	**R1, R2 and R3 long chain alkyl group Main carbon group C16 and C18**
Soybean Oil	**Soybean Oil**	**None**			**871 g/mol**	**R1, R2 and R3 long chain alkyl group Main carbon group C16 and C18**

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		5	Adequate		
	II			1	Adequate	3/27/2015	Review by Tarun Mehta

[1] Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents: None

18. STATUS:

ONDP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
EA	Categorical exclusion is granted	November 04, 2014	Tarun Mehta

The CMC Review for NDA 207648

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has ***not*** issued an "Acceptable" recommendation for this application.

Also, label/labeling issues are ***not*** satisfactorily resolved as of this review.

Therefore, from the ONDP perspective, this NDA is ***not*** ready for approval in its present form per 21CFR 314.125(b)(6),(13) until above pending issues are satisfactorily resolved.

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

Not applicable

II. Summary of CMC Assessments

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

The proposed SmoFlipid is a new addition to currently marketed lipid injectable emulsion products; Intralipid 20%, Kabiven, Clinolipid. These products are based on two active ingredients, Soybean Oil and Olive Oil. (b) (4)

(b) (4)

Because of added two *new active ingredients*, MCT (NF) and Fish Oil (USP, Dietary Supplement), to the currently approved products, an NME issue was raised, and after lengthy discussions with regulatory experts in this area (see the **Attachment 2**), it was decided that this product is not an NME due to the fact that their active moieties (fatty acids) were parts of the previously approved products including those withdrawn from the market.

To comply with Agency's mandate for heavy metal controls on LVP products, nine heavy metals (b) (4) were controlled with acceptance criteria. These acceptance criteria are deemed adequate, although there are some very minor differences from the numbers calculated based on the PDE set by ICH Q3D (see the section ***P.5.5***).

Phytosterols are also controlled with acceptable levels.

(1) Drug Substances

The drug product, Smoflipid 20%, contains four different active ingredients: Soybean Oil, USP; Medium Chain Triglycerides (MCT), NF; Olive Oil, NF; and Fish Oil, USP Dietary Supplement.

These active ingredients are prepared (b) (4) (b) (4) CMC information for each active ingredient provided in this application is found adequate. All of these active ingredients are supplied by the applicant except for MCT, which is also supplied by another supplier with a DMF (b) (4) The DMF is deemed adequate.

(2) Drug Products

Smoflipid 20% is a sterile parenteral nutrition product intended for intravenous administration and it is composed of Soybean Oil (USP) 6g; Medium Chain Triglycerides (MCT, NF), 6g; Olive Oil (NF) 5g; and Fish Oil (USP Dietary Supplement), 3g, and other excipients; all-rac-a-tocopherol, purified egg phospholipids, glycerol, and sodium oleate.

The drug product is available in three packaging sizes: 100mL, 250mL and 500mL, and is packaged in an one-chamber-bag (1-CB), which is made of (b) (4) (b) (4)

The drug product is manufactured (b) (4) .

The drug product is tested for triglycerides, glycerol, phospholipids, free fatty acids, and pH in accordance with USP monograph for Lipid Injectable Emulsions. It is also tested for globule size/distribution per USP <729> . The elemental impurities were analyzed based on USP <233> and the acceptance levels are proposed in line with ICH Q3D.

The drug product specification is deemed **adequate**.

The stability data show that the drug product met the proposed specification for 24 months at the proposed storage condition in the commercial packaging system, and the proposed 24 month expiry dating period is granted.

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

The drug product is dosed as intravenous infusion for a source of calories, and essential fatty acids for patients requiring parenteral nutrition.

C. Basis for Not-Approval Recommendation

2. 21CFR 314.125(b)(13)
   - The Office of Compliance has ***not*** issued an overall ***"Acceptable"*** recommendation for the application

3. 21CFR 314.125(b)(6)
   - Labels/labeling do ***not*** have an adequate information including the established name.

(see the **List of deficiencies** on p. 130)

III. Administrative

A. Reviewer's Signature:

Digitally signed by Tarun D. Mehta -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tarun D. Mehta -S, 0.9.2342.19200300.100.1.1=1300364542
Date: 2015.05.26 16:11:54 -04'00'

Tarun Mehta, M.Sc.

B. Endorsement Block:

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2015.05.26 16:14:28 -04'00'

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch V/DNDP II, ONDP

C. CC Block: entered electronically in DFS

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

SMOFlipid 20%(lipid injectable emulsion)

A. Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

(b) (4)

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	**SMOFLIPID (lipid injectable emulsion) 20% for intravenous use Satisfactory**
Dosage form, route of administration	Emulsion, Injectable, Satisfactory
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (201.57(a)(8))	Emulsion; Strength: 20% Satisfactory
Whether the drug product is scored	NA

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths

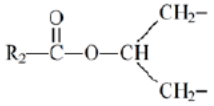
(b) (4)

Item	Information Provided in NDA
Available dosage forms	Emulsion **Satisfactory**
Strengths: in metric system	0.2g/mL of emulsion **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Smoflipid is a lipid injectable emulsion for IV infusion available in 100 mL, 250 mL, and 500 mL bags. **Satisfactory**

#11: Description

(b) (4)

CMC Assessment Section

Item	Information Provided in NDA
Proprietary name and established name	**SMOFLIPID** **Not Satisfactory**
Dosage form and route of administration	Emulsion, Intravenous **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	NA
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	1.2 g egg phospholipids, 2.5 g glycerin, 16.3 to 22.5 mg all-*rac*-α-tocopherol, 0.3 g sodium oleate, water for injection and sodium hydroxide for pH adjustment **Satisfactory**
Statement of being sterile (if applicable)	Yes **Satisfactory**
Pharmacological/ therapeutic class	TPN **Satisfactory**
Chemical name, structural formula, molecular weight	 where R
Linoleic A $C_{18}H_{32}O_2$ **Caprylic A** $C_8H_{16}O_2$ **Capric Aci** $C_{10}H_{20}O_2$	

Linolenic Acid $C_{18}H_{30}O_2$ **EPA** $C_{20}H_{30}O_2$ **DHA** $C_{22}H_{32}O_2$ **Not Satisfactory**	
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Smoflipid has an osmolality of approximately 380 mOsm/kg water pH adjustment (pH 6 to 9). **Satisfactory**

Evaluation:

The name, **SmoFlipid** should be revised as **Smoflipid (lipid injectable emulsion) 20%**

#16: How Supplied/Storage and Handling

SMOFlipid should be stored at 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature. Avoid excessive heat. Do not freeze. If accidentally frozen, discard bag. Store in overpouch until intended for use.

After removing the overpouch, SMOFlipid should be infused immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. If not used immediately, storage should not be longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage (b) (4) (b) (4) the product should be infused within 24 hours.

CMC Assessment Section

Item	Information Provided in NDA
Strength of dosage form	20% **Satisfactory**
Available units (e.g., bottles of 100 tablets)	100 mL, 250 mL, and 500mL bag **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	SMOFLIPID is a sterile, lipid injectable emulsion in following (b) (4) bags: NDC: 63323-820-00 (100 mL) 10bags/box NDC: 63323-820-74 (250 mL) 10bags/box NDC: 63323-820-50 (500 mL) 12bags/box **Satisfactory**
Special handling (e.g., protect from light)	The bag is packaged in an (b) (4) overpouch, which contains an oxygen absorber / oxygen indicator sachet. Smoflipid should be stored at 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature. Avoid excessive heat. Do not freeze. If accidentally frozen, discard the drug product. Store in overpouch until ready for use. After removing the overpouch, Smoflipid should be infused immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. If not used immediately, storage should not be longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage (b) (4) (b) (4) the product should be infused within 24 hours. Admixtures containing Smoflipid should be infused immediately. If not used immediately, the product should not be stored longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage, the emulsion should be infused within 24 hours. **Satisfactory**
Storage conditions	It is recommended that the product be stored at room temperature (25°C/77°F) **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by: Fresenius Kabi, Uppsala, Sweden **Satisfactory**

Evaluation:
The name, **SmoFlipid** should be revised as **Smoflipid (lipid injectable emulsion) 20%**

2. Immediate container labels

Similar packaging are also provided in NDA for 100mL and 250mL bags.

Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Establish name is not correct, font are ok **Not Satisfactory**
Dosage strength	Yes
Net contents	Yes
"Rx only" displayed prominently on the main panel	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes
Lot number and expiration date (21 CFR 201.17)	Yes (Block)
Storage conditions	Yes
Bar code (21CFR 201.25)	Yes
Name of manufacturer/distributor	Yes
And others, if space is available	Energy: 1000kcal/500mL

Evaluation: **Inadequate**

The drug name should be revised as follows:

Smoflipid (lipid injectable emulsion, USP) 20%
100g/500mL (0.2g/mL)

3. Carton labeling:

Evaluation: NA

B. **Environmental Assessment Or Claim Of Categorical Exclusion**

The applicant has made following statement on environment compliance:

"Fresenius Kabi states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of SMOFlipid 20% at its facility in Uppsala, Sweden, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of SMOFlipid 20% at its facility in Uppsala, Sweden".

Adequate

III. List Of Deficiencies:

A. Regarding CMC
None

B. Regarding GMP inspection
- The Office of Compliance has not issued a final recommendation.

C. Regarding labels/labeling
- The drug name should be revised as follows:

Smoflipid (lipid injectable emulsion, USP) 20%
100g/500mL (0.2g/mL)

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CMC Review Data Sheet

NDA 207648

Smoflipid (Lipid Injectable Emulsion) 20%, USP

Fresenius Kabi USA, LLC

Tarun Mehta

Review Chemist

Division of New Drug Products II
Branch V
Office of New Drug Products

CMC REVIEW OF NDA 207648
For the Division of Gastroenterology Products (HFD-180)

(Please add page numbers in the review and fix the TOA with correct page numbers)

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4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
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Amendment 0010	March 19, 2015
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7. NAME & ADDRESS OF APPLICANT:

Name:	Fresenius Kabi USA, LLC
Address:	Three Corporate Drive Lake Zurich, IL 60047
Representative:	Lakshmi Rebbapragada, Sr. Regulatory Specialist
Telephone:	(847) 550-2399

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SMOFlipid 20%
b) Non-Proprietary Name: Lipid Injectable Emulsion, USP
c) Code Name/# (ONDP only): None
d) Chem. Type/Submission Priority (ONDP only):
- Chem. Type: 2

- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Parenteral nutrition

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: 20% w/v

13. ROUTE OF ADMINISTRATION: Intravenous infusion

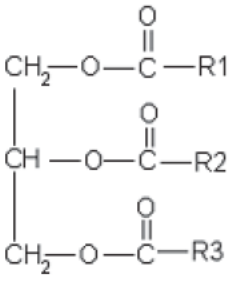
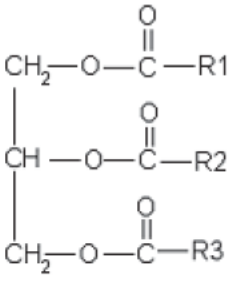
14. Rx/OTC DISPENSED: __√__ Rx ___OTC

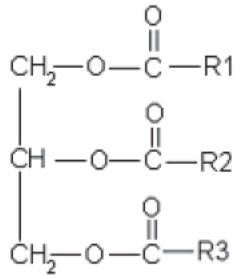
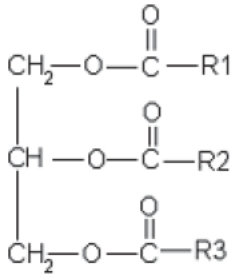
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

√ Not a SPOTS product

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

Chemical names, compendial names, structural formulas, abbreviations for active ingredients:

Chemical Name/ USP name	INN/IUPAC name	Abbreviation	structural formula	MW g/mol	MF
Fish Oil	**Fish Oil**	**None**		**879 g/mol**	**R1, R2 and R3 long chain alkyl group C18, C20,c21 and C22**
Medium Chain Triglycerides **Source: Coconut and Palm Kernels**	**Caprylic and Capric triglycerides**	**None**		**505 g/mol**	**R1, R2 and R3 long chain alkyl group C6,C8,C10, C12 and C14 Major C8 and C10)**

Olive Oil	**None**	**None**			**861 g/mole**	**R1, R2 and R3 long chain alkyl group Main carbon group C16 and C18**
Soybean Oil	**Soybean Oil**	**None**			**871 g/mol**	**R1, R2 and R3 long chain alkyl group Main carbon group C16 and C18**

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents: None

18. STATUS:

ONDP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
EA	Categorical exclusion is granted	November 04, 2014	Tarun Mehta

The CMC Review for NDA 207648

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has ***not*** issued an "Acceptable" recommendation for this application.

Also, label/labeling issues are ***not*** satisfactorily resolved as of this review.

Therefore, from the ONDP perspective, this NDA is ***not*** ready for approval in its present form per 21CFR 314.125(b)(6),(13) until above pending issues are satisfactorily resolved.

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

Not applicable

II. Summary of CMC Assessments

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

The proposed SmoFlipid is a new addition to currently marketed lipid injectable emulsion products; Intralipid 20%, Kabiven, Clinolipid. These products are based on two active ingredients, Soybean Oil and Olive Oil. (b) (4)

Because of added two *new active ingredients*, MCT (NF) and Fish Oil (USP, Dietary Supplement), to the currently approved products, an NME issue was raised, and after lengthy discussions with regulatory experts in this area (see the **Attachment 2**), it was decided that this product is not an NME due to the fact that their active moieties (fatty acids) were parts of the previously approved products including those withdrawn from the market.

To comply with Agency's mandate for heavy metal controls on LVP products, nine heavy metals (b) (4) were controlled with acceptance criteria. These acceptance criteria are deemed adequate, although there are some very minor differences from the numbers calculated based on the PDE set by ICH Q3D (see the section ***P.5.5***).

Phytosterols are also controlled with acceptable levels.

(1) Drug Substances

The drug product, Smoflipid 20%, contains four different active ingredients: Soybean Oil, USP; Medium Chain Triglycerides (MCT), NF; Olive Oil, NF; and Fish Oil, USP Dietary Supplement.

These active ingredients are prepared (b) (4)

CMC information for each active ingredient provided in this application is found adequate. All of these active ingredients are supplied by the applicant except for MCT, which is also supplied by another supplier with a DMF (b) (4) The DMF is deemed adequate.

(2) Drug Products

Smoflipid 20% is a sterile parenteral nutrition product intended for intravenous administration and it is composed of Soybean Oil (USP) 6g; Medium Chain Triglycerides (MCT, NF), 6g; Olive Oil (NF) 5g; and Fish Oil (USP Dietary Supplement), 3g, and other excipients; all-rac-a-tocopherol, purified egg phospholipids, glycerol, and sodium oleate.

The drug product is available in three packaging sizes: 100mL, 250mL and 500mL, and is packaged in an one-chamber-bag (1-CB), which is made of (b) (4)

The drug product is manufactured (b) (4)

The drug product is tested for triglycerides, glycerol, phospholipids, free fatty acids, and pH in accordance with USP monograph for Lipid Injectable Emulsions. It is also tested for globule size/distribution per USP <729> . The elemental impurities were analyzed based on USP <233> and the acceptance levels are proposed in line with ICH Q3D.

The drug product specification is deemed **adequate**.

The stability data show that the drug product met the proposed specification for 24 months at the proposed storage condition in the commercial packaging system, and the proposed 24 month expiry dating period is granted.

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

The drug product is dosed as intravenous infusion for a source of calories, and essential fatty acids for patients requiring parenteral nutrition.

C. Basis for Not-Approval Recommendation

2. 21CFR 314.125(b)(13)
   - The Office of Compliance has ***not*** issued an overall ***"Acceptable"*** recommendation for the application

3. 21CFR 314.125(b)(6)
   - Labels/labeling do ***not*** have an adequate information including the established name.

(see the **List of deficiencies** on p. 130)

III. Administrative

A. Reviewer's Signature:

Digitally signed by Tarun D. Mehta -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tarun D. Mehta -S, 0.9.2342.19200300.100.1.1=1300364542
Date: 2015.05.26 16:11:54 -04'00'

Tarun Mehta, M.Sc.

B. Endorsement Block:

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2015.05.26 16:14:28 -04'00'

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch V/DNDP II, ONDP

C. CC Block: entered electronically in DFS

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

SMOFlipid 20%(lipid injectable emulsion)

A. Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

(b) (4)

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	**SMOFLIPID (lipid injectable emulsion) 20% for intravenous use Satisfactory**
Dosage form, route of administration	Emulsion, Injectable, Satisfactory
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (201.57(a)(8))	Emulsion; Strength: 20% Satisfactory
Whether the drug product is scored	NA

(b) "Full Prescribing Information" Section

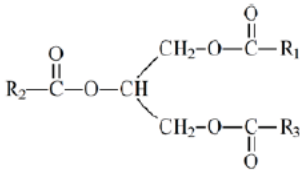
 # 3: Dosage Forms and Strengths

(b) (4)

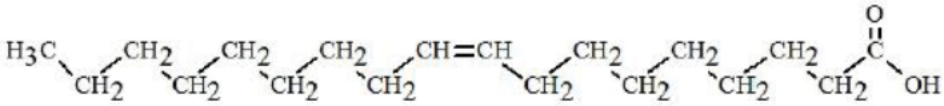
Item	Information Provided in NDA
Available dosage forms	Emulsion **Satisfactory**
Strengths: in metric system	0.2g/mL of emulsion **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Smoflipid is a lipid injectable emulsion for IV infusion available in 100 mL, 250 mL, and 500 mL bags. **Satisfactory**

#11: Description

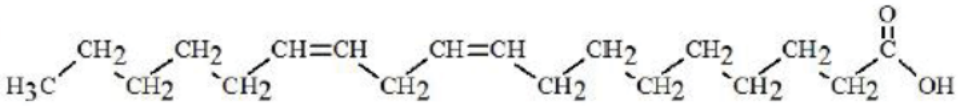
(b) (4)

Item	Information Provided in NDA
Proprietary name and established name	**SMOFLIPID** **Not Satisfactory**
Dosage form and route of administration	Emulsion, Intravenous **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	NA
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	1.2 g egg phospholipids, 2.5 g glycerin, 16.3 to 22.5 mg all-*rac*-α-tocopherol, 0.3 g sodium oleate, water for injection and sodium hydroxide for pH adjustment **Satisfactory**
Statement of being sterile (if applicable)	Yes **Satisfactory**
Pharmacological/ therapeutic class	TPN **Satisfactory**
Chemical name, structural formula, molecular weight	 where $R_1\overset{O}{\overset{\|}{C}}O-$, $R_2\overset{O}{\overset{\|}{C}}O-$, and $R_3\overset{O}{\overset{\|}{C}}O-$ are saturated and unsaturated fatty acid res

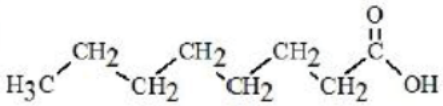
Oleic Acid
$C_{18}H_{34}O_2$



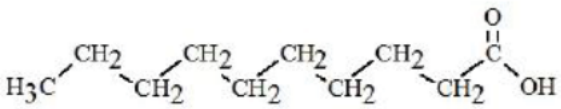
Linoleic Acid
$C_{18}H_{32}O_2$

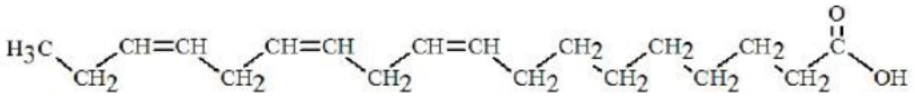
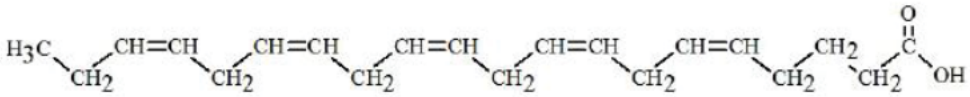
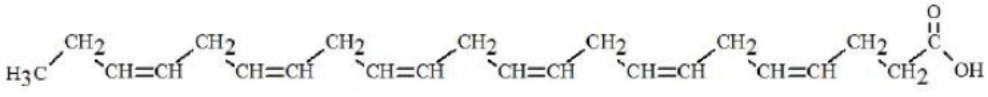


Caprylic Acid
$C_8H_{16}O_2$



Capric Acid
$C_{10}H_{20}O_2$



Linolenic Acid  **$C_{18}H_{30}O_2$** **EPA**  **$C_{20}H_{30}O_2$** **DHA**  **$C_{22}H_{32}O_2$** **Not Satisfactory**	
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Smoflipid has an osmolality of approximately 380 mOsm/kg water pH adjustment (pH 6 to 9). **Satisfactory**

Evaluation:

The name, **SmoFlipid** should be revised as **Smoflipid (lipid injectable emulsion) 20%**

#16: How Supplied/Storage and Handling

SMOFlipid should be stored at 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature. Avoid excessive heat. Do not freeze. If accidentally frozen, discard bag. Store in overpouch until intended for use.

After removing the overpouch, SMOFlipid should be infused immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. If not used immediately, storage should not be longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage (b) (4) the product should be infused within 24 hours.

CMC Assessment Section

Item	Information Provided in NDA
Strength of dosage form	20% **Satisfactory**
Available units (e.g., bottles of 100 tablets)	100 mL, 250 mL, and 500mL bag **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	SMOFLIPID is a sterile, lipid injectable emulsion in following (b) (4) bags: NDC: 63323-820-00 (100 mL) 10bags/box NDC: 63323-820-74 (250 mL) 10bags/box NDC: 63323-820-50 (500 mL) 12bags/box **Satisfactory**
Special handling (e.g., protect from light)	The bag is packaged in an (b) (4) overpouch, which contains an oxygen absorber / oxygen indicator sachet. Smoflipid should be stored at 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature. Avoid excessive heat. Do not freeze. If accidentally frozen, discard the drug product. Store in overpouch until ready for use. After removing the overpouch, Smoflipid should be infused immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. If not used immediately, storage should not be longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage (b) (4) (b) (4) the product should be infused within 24 hours. Admixtures containing Smoflipid should be infused immediately. If not used immediately, the product should not be stored longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage, the emulsion should be infused within 24 hours. **Satisfactory**
Storage conditions	It is recommended that the product be stored at room temperature (25°C/77°F) **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by: Fresenius Kabi, Uppsala, Sweden **Satisfactory**

Evaluation:
The name, **SmoFlipid** should be revised as **Smoflipid (lipid injectable emulsion) 20%**

2. **Immediate container labels**

Similar packaging are also provided in NDA for 100mL and 250mL bags.

Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Establish name is not correct, font are ok **Not Satisfactory**
Dosage strength	Yes
Net contents	Yes
"Rx only" displayed prominently on the main panel	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes
Lot number and expiration date (21 CFR 201.17)	Yes (Block)
Storage conditions	Yes
Bar code (21CFR 201.25)	Yes
Name of manufacturer/distributor	Yes
And others, if space is available	Energy: 1000kcal/500mL

Evaluation: **Inadequate**

The drug name should be revised as follows:

Smoflipid (lipid injectable emulsion, USP) 20%
100g/500mL (0.2g/mL)

3. Carton labeling:

Evaluation: NA

B. **Environmental Assessment Or Claim Of Categorical Exclusion**

The applicant has made following statement on environment compliance:

"Fresenius Kabi states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of SMOFlipid 20% at its facility in Uppsala, Sweden, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of SMOFlipid 20% at its facility in Uppsala, Sweden".

Adequate

III. List Of Deficiencies:

A. Regarding CMC
None

B. Regarding GMP inspection
- The Office of Compliance has not issued a final recommendation.

C. Regarding labels/labeling
- The drug name should be revised as follows:

Smoflipid (lipid injectable emulsion, USP) 20%
100g/500mL (0.2g/mL)

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Product Quality Microbiology Review

08 May 2015

NDA: 207648

Drug Product Name
Proprietary: SMOFlipid 20%
Non-proprietary: Lipid Injectable Emulsion, USP

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
25 SEP 2014	26 SEP 2014	06 OCT 2014	09 OCT 2014
19 MAR 2015	15 MAR 2015	N/A	N/A
31 MAR 2015	31 MAR 2015	N/A	N/A
21 APR 2015	21 APR 2015	N/A	N/A

Applicant/Sponsor
Name: Fresenius Kabi USA, LLC
Address: Three Corporate Drive, Lake Zurich, IL 60047
Representative: Lakshmi Rebbapragada
Telephone: 847-550-2399

Name of Reviewer: Erika Pfeiler, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(1)

2. SUBMISSION PROVIDES FOR: Initial marketing of a sterile drug product

3. MANUFACTURING SITE:
Fresenius Kabi AB, Uppsala, Sweden

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
Sterile emulsion
Intravenous infusion
20%

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Parenteral nutrition

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS: N/A

filename: 207648.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Product is (b) (4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
(b) (4)				5	5	175	(b) (4)
Endo		4		4	4	64	

1 = (b) (4)

2 = (b) (4)

3 = (b) (4)

4 = (b) (4)

5 = (b) (4)

6 = RPN = O(after modification when applicable)×S×D

RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

B. Final Risk Assessment – The applicant has proposed an adequate strategy to mitigate risk.

IV. Administrative

A. Reviewer's Signature _____

Erika Pfeiler, Ph.D.
Microbiologist

B. Endorsement Block_____

Stephen Langille, Ph.D.
Acting Branch Chief

C. CC Block

N/A

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Erika A. Pfeiler -S

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Date: 2015.05.08 10:11:27 -04'00'

Stephen E. Langille -A

Digitally signed by Stephen E. Langille -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151320, cn=Stephen E. Langille -A
Date: 2015.05.14 09:56:27 -04'00'

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **207648**

2. DATES AND GOALS:

Letter Date: 9/25/2014	Submission Received Date : 10/6/2014
PDUFA Goal Date: 7/26/2015	IQA date 12/5/2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	**SMOFLIPID 20%**
Established or Non-Proprietary Name (USAN):	**lipid injectable emulsion (USP monograph)**
Dosage Form:	**emulsion for infusion**
Route of Administration	**intravenous**
Strength/Potency	**20%**
Rx/OTC Dispensed:	**Rx**

4. INDICATION: (b) (4)

5. DRUG SUBSTANCE:
fatty acids derived from four different oils: soybean oil (6%), medium chain triglycerides (6%), olive oil (5%), and fish oil (3%) [See page 6 for structures.]

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

Fresenius Kabi USA, LLC

7. SUBMISSION PROPERTIES:

Review Priority:	no
Submission Classification (Chemical Classification Code):	Type 2 (see page 6 for additional information)
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Gastrointestinal and Inborn Error Products (HFD-180)

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Clinical Pharmacology			(included in review team)
Establishment Evaluation Request (EER)	x		Already requested
Pharmacology/Toxicology			(included in review team)
Methods Validation		x	
Environmental Assessment	x		Categorical exclusion
CDRH		x	
Other		x	

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?
Yes √ No

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
Yes √ No
Comments for 74-Day Letter: none

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? NO BIOPHARM REVIEW IS REQUIRED

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?
Yes √ No
Comments were sent out in the 74-Day Letter

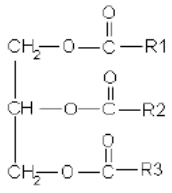
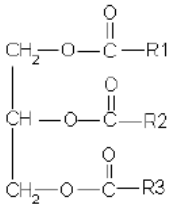
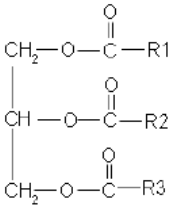
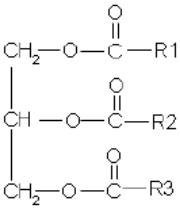
Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
no	yes	no	no

Is a team review recommended?	Yes
Assigned Reviewers:	CMC: Tarun, Mehta Microbiology: Erika Pfeifer Office of Compliance: Christina Capacci-Daniel

Application Highlights

SMOFlipid 20% is an intravenous lipid emulsion for use in Parenteral Nutrition. This product, which was developed under IND 102137, is a mixture of four different oils, whose structures are given below: soybean oil (6%), medium chain triglycerides (6%), olive oil (5%), and fish oil (3%).

Soybean oil	 R = Fatty acid chains	Triacylglycerol with fatty acid chains mainly C16:0, C18:1, C18:2, C18:3
Medium chain triglycerides (MCT)	 R = Fatty acid chains	Triacylglycerol with fatty acid chains mainly C8:0, C10:0
Olive oil	 R = Fatty acid chains	Triacylglycerol with fatty acid chains mainly C16:0, C18:1, C18:2
Fish oil	 R = Fatty acid chains	Triacylglycerol with fatty acid chains mainly C20:5, C22:6

While the active ingredients in SMOFlipid are soybean oil, medium-chain triglycerides (MCT), olive oil, and fish oil, it is the fatty acids (present as their triglycerides) that are the source of nutrition, i.e. the active moieties. A comparison of the fatty acid composition (%) for each of the oils used to manufacture SMOFlipid is provided below.

Fatty acid	Carbon chain length	Number of double bonds	Olive, USP	Soy, USP	Fish oil (USP Dietary Supplements monograph)	Medium chain triglycerides USP
Palmitic	16	0	(b) (4)			
Stearic	18	0				
Oleic	18	1				
Linoleic	18	2				
Linolenic	18	3				
caprylic	8	0				(b) (4)
capric	10	0	(b) (4			
eicosapentaenoic	20	5				
docosahexaenoic	(b) (4)	6				
Total omega-3-acids*						

*includes α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid, all of which are polyunsaturated.

There are no new molecular entities (NMEs) in this product. Since both olive and soy oil are used in approved TPN products (Intralipid and ClinoLipid), none of the fatty acids in SmoFlipid derived from olive oil or soybean oil can be considered NMEs. Similarly, eicosapentaenoic and docosahexaenoic acid (the major fatty acids components from fish oil) cannot be considered (NMEs) in SmoFlipid, because these two omega-3 fatty acids have been approved in products such as Lovaza and Epanova. And finally, although MCT is a new active ingredient, its two major fatty acid components, caprylic and capric acids, were approved in the 1940's and 1950s (see email chain on page 7 of this document) and cannot be considered NMEs. Since they are present in SmoFlipid as triglyceride esters, but were approved as the free carboxylic acids or salts, this application is classified as a *Type 2.*

The above arguments were presented to the ONDQA Precedence Committee on July 1, 2013, at which time the committee agreed with the decision to classify this application as a *Type 2.*

From: Schmuff, Norman R
Sent: Wednesday, July 17, 2013 9:40 AM
To: Pope Miksinski, Sarah
Cc: Kowblansky, Marie; Rhee, Moo Jhong
Subject: RE: SMOFlipid

I concur. Since all of the active moieties have been approved previously, it's not an NME.

Norman

From: Pope Miksinski, Sarah
Sent: Wednesday, July 17, 2013 9:21 AM
To: Schmuff, Norman R
Cc: Kowblansky, Marie; Rhee, Moo Jhong
Subject: FW: SMOFlipid

Norman,
Do you have any concerns with the revised recommendation?

Sarah

From: Kowblansky, Marie
Sent: Monday, July 15, 2013 11:04 AM
To: Griebel, Donna; Berry, Karyn; Gottlieb, Klaus; Mulberg, Andrew; Brancazio, Matthew (FDA)
Cc: Rhee, Moo Jhong; Pope Miksinski, Sarah; Beitz, Julie G; Walsh, Maria R; Schmuff, Norman R
Subject: SMOFlipid

Based on the email below, we are revising our previous decision and conclude that SMOFlipid will not be treated as an NME application. This information that the capric and caprylic components have been previously approved, came from a remote data base to which it appears that only one person has access.

From: Jones, Michael D
Sent: Friday, July 12, 2013 10:29 AM
To: Schmuff, Norman R; Kowblansky, Marie
Cc: Folkendt, Michael M; Rhee, Moo Jhong; Friedman, Beverly J; Jones, Ashley R; Parks, Donal; Schwemer, Tawni; Stronati, Katherine
Subject: RE: Old NDAs - Carprylic/Capric (octanoic/capric acid)

What all do you need to know.
Looks like:

1. NDA 9540 was approved in 54 and wd by fr notice 6aug71. Probably didn't make it thru DESI.
2. 6808 was approved in 49 and wd 24jul70, again, may not have made it thru DESI.

By the way, 6096 has (b) (4) as actives, approved in 48, and the application looks like it was wd 6-7-82. If wd in 82, may have gone thru DESI.

And we have approved capric acid as well. See NDa 11739 which was approved in 58 and was wd 24July1970. May not have gone thru DESI.

So … bottom line, looks like both caprilyic and capric were "approved", as active ingredients, but may not have gone thru DESI.

ONDQA Initial Quality Assessment (IQA) and Filing Review

Mike

Application #:	Submission Type:	Established/Proper Name:
NDA (b) (4)	original	Lipid injectable emulsion
Applicant:	**Letter Date:**	**Dosage Form:**
Fresenius Kabi	9/26/14	emulsion
Chemical Type:	**Stamp Date:**	**Strength:**
Type 2	9/26/14	20%

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	x		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			no

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]		x	
2.	Botanical[1]		x	
3.	Naturally-derived Product		x	
4.	Narrow Therapeutic Index Drug		x	
5.	PET Drug		x	
6.	PEPFAR Drug		x	
7.	Sterile Drug Product		x	
8.	Transdermal[1]		x	
9.	Pediatric form/dose[1]		x	
10.	Locally acting drug[1]		x	
11.	Lyophilized product[1]		x	
12.	First generic[1]		x	
13.	Solid dispersion product[1]		x	
14.	Oral disintegrating tablet[1]		x	

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
15.	Modified release product[1]		x	
16.	Liposome product[1]		x	
17.	Biosimiliar product[1]		x	
18.	Combination Product _____		x	
19.	Other_____		x	

Regulatory Considerations					
20.	USAN Name Assigned		x		Established name is USP monograph name
21.	End of Phase II/Pre-NDA Agreements		x		
22.	SPOTS (Special Products On-line Tracking System)			x	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application			x	
24.	Comparability Protocol(s)[2]			x	
25.	Other_____			x	
Quality Considerations					
26.	Drug Substance Overage			x	
27.	Design Space	Formulation		x	
28.		Process		x	
29.		Analytical Methods		x	
30.		Other		x	
31.	Real Time Release Testing (RTRT)			x	
32.	Parametric Release in lieu of Sterility Testing			x	
33.	Alternative Microbiological Test Methods			x	
34.	Process Analytical Technology[1]			x	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product		x	
36.		Excipients		x	
37.		Microbial		x	
38.	Unique analytical methodology[1]			x	
39.	Excipients of Human or Animal Origin			x	
40.	Novel Excipients			x	
41.	Nanomaterials[1]			x	
42.	Hold Times Exceeding 30 Days			x	
43.	Genotoxic Impurities or Structural Alerts			x	
44.	Continuous Manufacturing			x	
45.	Other unique manufacturing process[1]			x	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).			x	
47.	New delivery system or dosage form[1]			x	
48.	Novel BE study designs			x	
49.	New product design[1]			x	
50.	Other_____			x	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	x			

C. FILING CONSIDERATIONS					
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	x			
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	x			
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	x			
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	x			For medium chain triglycerides (drug substance) (b) (4), all information is referenced to DMF (b) (4) For the other oils, the required information is included directly in the NDA
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a	x			

C. FILING CONSIDERATIONS					
	review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients	X			

C. FILING CONSIDERATIONS					
	❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?			x	No Biopharm review required
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*			x	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.			x	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?			x	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?			x	

C. FILING CONSIDERATIONS					
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?			x	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?			x	
15.	Are Executed Batch Records for the drug product available?	x			
16.	Is the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients			x	
17.	Is the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			x	

See appended electronic signature page}

Marie Kowblansky, PhD
CMC-Lead
Division II
Office of New Drug Quality Assessment

ONDQA Initial Quality Assessment (IQA) and Filing Review

From: Schmuff, Norman R
Sent: Wednesday, July 17, 2013 9:40 AM
To: Pope Miksinski, Sarah
Cc: Kowblansky, Marie; Rhee, Moo Jhong
Subject: RE: SMOFlipid

I concur. Since all of the active moieties have been approved previously, it's not an NME.

Norman

From: Pope Miksinski, Sarah
Sent: Wednesday, July 17, 2013 9:21 AM
To: Schmuff, Norman R
Cc: Kowblansky, Marie; Rhee, Moo Jhong
Subject: FW: SMOFlipid

Norman,
Do you have any concerns with the revised recommendation?

Sarah

From: Kowblansky, Marie
Sent: Monday, July 15, 2013 11:04 AM
To: Griebel, Donna; Berry, Karyn; Gottlieb, Klaus; Mulberg, Andrew; Brancazio, Matthew (FDA)
Cc: Rhee, Moo Jhong; Pope Miksinski, Sarah; Beitz, Julie G; Walsh, Maria R; Schmuff, Norman R
Subject: SMOFlipid

Based on the email below, we are revising our previous decision and conclude that SMOFlipid will not be treated as an NME application. This information that the capric and caprylic components have been previously approved, came from a remote data base to which it appears that only one person has access.

From: Jones, Michael D
Sent: Friday, July 12, 2013 10:29 AM
To: Schmuff, Norman R; Kowblansky, Marie
Cc: Folkendt, Michael M; Rhee, Moo Jhong; Friedman, Beverly J; Jones, Ashley R; Parks, Donal; Schwemer, Tawni; Stronati, Katherine
Subject: RE: Old NDAs - Carprylic/Capric (octanoic/capric acid)

What all do you need to know.
Looks like:

3. NDA 9540 was approved in 54 and wd by fr notice 6aug71. Probably didn't make it thru DESI.
4. 6808 was approved in 49 and wd 24jul70, again, may not have made it thru DESI.

By the way, 6096 has [redacted] (b) (4) as actives, approved in 48, and the application looks like it was wd 6-7-82. If wd in 82, may have gone thru DESI.

And we have approved capric acid as well. See NDa 11739 which was approved in 58 and was wd 24July1970. May not have gone thru DESI.

So … bottom line, looks like both caprilyic and capric were "approved", as active ingredients, but may not have gone thru DESI.

Mike

ONDQA Initial Quality Assessment (IQA) and Filing Review

NDA RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• raw materials • process parameters	L			
Particulate matter	• Formulation • container/closure • Process parameters • scale/equipment • raw material	M			
Sterility	• Formulation • container/closure • Process parameters • scale/equipment	H			
droplet size distribution (suspension)	• Formulation • scale/equipment	M			
pH	• Formulation • container/closure • Process parameters • scale/equipment • raw material	L			

ONDQA Initial Quality Assessment (IQA) and Filing Review

IQA RISK ASSESSMENT

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment	Risk
Assay, stability	• raw materials • process parameters	2	2	1	4		L
Particulate matter	• Formulation • container/closure • Process parameters • scale/equipment • raw material	3	3	5	45		M
Sterility	• Formulation • container/closure • Process parameters • scale/equipment	4	5	5	100		H
droplet size distribution (suspension)	• Formulation • scale/equipment	3	3	3	27		M
pH	• Formulation • container/closure • Process parameters • scale/equipment • raw material	3	4	1	12		L

Marie Kowblansky -S

Digitally signed by Marie Kowblansky -S
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Date: 2014.12.12 12:49:15 -05'00'

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 207648 **Applicant:** Fresenius Kabi USA LLC **Letter Date:** 25 September 2014

Drug Name: SMOFlipid 20% **NDA Type:** 505(b)(1) **Stamp Date:** 26 September 2014

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?			The submission is in English.
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		(b) (4) [redacted]
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?		X	See Additional Comments.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: This application describes a sterile emulsion for intravenous infusion. The product may be mixed with amino acid and dextrose injections prior to infusion. Proposed labeling states that if such an admixture is not used immediately, it may be held at 2-8°C for 24 hours, and once removed from refrigerated storage, must be used within 24 hours. No data were provided to support the proposed hold times. While the 24-hour storage period at 2-8°C is acceptable without supporting data, the 24-hour period following removal from storage should

be shortened to 4 hours. A comment will be sent to the sponsor to convey this information, along with other routine information requests.

Erika Pfeiler, Ph.D. Date
Microbiologist

Stephen Langille, Ph.D. Date
Senior Review Microbiologist

The following information requests should be conveyed to the applicant in the 74-day letter:

1. Your proposed product labeling states that an admixture of the drug product with amino acids and dextrose may be held at 2-8°C and must be used within 24 hours following removal from refrigerated storage. [redacted], you should limit the post-admixture room temperature hold time to 4 hours.
2. Your application describes container closure testing performed on the [redacted] bags using a microbial ingress testing method. While your test method adequately demonstrates that the bag is capable of maintaining product sterility, it is unclear if your method is adequate to demonstrate that sterility is maintained throughout the entire fluid path of the container closure (including the injection and infusion ports). Provide additional information to support that container closure integrity is maintained through the entire fluid path of the drug product.
3. Your application states [redacted] Your sterilization process validation information states that these studies were performed [redacted] While it is acceptable for you to validate the sterilization process [redacted] you must demonstrate that [redacted] the drug product are appropriately qualified. Provide information from your three most recent qualification/requalification studies [redacted] for drug product sterilization.
4. Your application alternately states that the maximum allowed [redacted] bioburden is [redacted] CFU/unit or ≤ [redacted] CFU/100 mL (Control of Critical Steps and Intermediates section). Clarify the [redacted] bioburden for your drug product.
5. Your application states that each drug product batch is subjected to a [redacted] test. Provide more information on this test, including a description of test methods and test acceptance criteria.
6. In your Description of Manufacturing Process and Process Controls section, you state that drug product [redacted] Clarify the sterilization parameters used for your drug product in production.

7. Your application describes [redacted] studies to validate the sterilization cycle for your drug product. Address the following points:
    a. Were these studies performed [redacted]?
    b. State the [redacted] studies. Provide a justification [redacted]
    c. State acceptance criteria for [redacted] studies.
    d. Describe positive controls used in these studies.
    e. Describe the [redacted] procedures [redacted] used in these studies.
8. What is the requalification schedule [redacted]?
9. Your application briefly describes a study [redacted] More information on this study is needed. Please submit a description of test methods, acceptance criteria, and test results.

Erika A. Pfeiler -S

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Date: 2014.11.10 11:05:19 -05'00'

Stephen E. Langille -A

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