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RESEARCH**

APPLICATION NUMBER:

207648Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD, MPH Deputy Director Division of Gastroenterology and Inborn Errors Products ODE III, CDER, FDA
Subject	Division Director Summary Review
NDA #	207648
Applicant Name	Fresenius Kabi
Date of Submission	September 26, 2014
PDUFA Goal Date	July 26, 2015 (revised-October 26, 2015) Goal date missed
Proprietary Name / Established (USAN) Name	Smoflipid Lipid injectable emulsion
Dosage Forms / Strength	For intravenous use 0.2 grams/mL
Proposed Indication(s)	Smoflipid is indicated in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated
Action/Recommended Action:	<i>Approval only in adults</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Karyn Berry
Statistical Review	Ben Vali
Pharmacology Toxicology Review	Emmanuel Akinshola
CMC Review/OBP Review	Tarun Mehta
OPQ/Microbiology Review	Erika Pfeiler
CDRH Reviewer	William Burdick
Clinical Pharmacology Review	Elizabeth Shang
Office of Scientific Investigations	Susan Leibenhaut, Joseph Peacock
CDTL Review	(Joyce Korvick – see signatory review)
DMEPA	Sherly Abraham
DMFH - Maternal Health Team	Carol Kasten
DMFH - Pediatric Health Team	Donna Snyder
Office of the Commissioner-Office of Pediatric Therapeutics	Gerri Baer
OPDP	Kathleen Klemm
CDRH	Alan Stevens

OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
OPQ = Office of Product Quality
CMC = Chemistry and Manufacturing
OPDP = Office of Prescription Drug Promotion
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL= Cross-Discipline Team Leader
CDRH = Center for Devices and Radiologic Health
DMFH= Division of Maternal Fetal Health

1. Introduction

Fresenius-Kabi submitted a New Drug Application # 207648 under 505(b)(1) of the FD&C Act on September 26, 2014 for Smoflipid (lipid injectable emulsion). A standard review was granted for this application when it was submitted since this drug product was not considered to contain a new molecular entity. In addition, at that time there were no drug shortages. A Major Amendment was received on June 29, 2015 that resulted in a 3-month review extension with a PDUFA goal date of October 26, 2015. This goal date was missed due to internal discussions on several aspects of this NDA which are discussed within this review.

Smoflipid is composed of four (b)(4) lipids: soybean oil, olive oil, medium chain triglycerides (MCT) and fish oil. Smoflipid is a lipid injectable emulsion, and the product complies with the USP monograph¹. The USP definition of lipid injectable emulsion is, in part, the following:

“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 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.”

The USP monograph requires that “[t]he label state [] the identity and the quantities of the specific oils in the Emulsion.”

Smoflipid is a 20% lipid injectable emulsion. It contains 6g/100mL soybean oil, 5g/100mL olive oil, 6g/100mL medium chain triglycerides (MCT), and 3g/100mL fish oil. During this review Smoflipid was determined to be a prescription fixed dose combination drug product.

Smoflipid provides (b)(4) the essential fatty acids linoleic acid (LA) and linolenic acid (ALA) (b)(4)

(b)(4) The applicant provided a rationale for the addition of two other oils contained in Smoflipid; MCT (b)(4) and fish oil (b)(4)

In addition, olive oil, includes long chain triglycerides (LCTs) rich in monounsaturated fatty acids (MUFAs), (b)(4)

¹ USP 38-NF, at 4109 (2015).

The applicant proposed that Smoflipid be indicated “as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated” (b) (4)

The proposed Smoflipid formulation is the same as the applicant’s “SMOFLipid,” which is approved and marketed outside the US and has been available since 2004. Important efficacy and safety issues discussed in this review include: 1.) essential fatty acid deficiency, 2.) potential liver toxicity due to the presence of phytosterols, 3.) elemental impurities.

2. Background

HISTORY

Lipid emulsions are primarily used as a source of calories (energy) and essential fatty acids. They are used in combination with amino acids, electrolytes, trace elements and dextrose in order to provide total parenteral nutrition. Intravenous lipid emulsions are used in patients with gastrointestinal dysfunction, who lack the capacity to absorb adequate nutrients to maintain or recover body mass and function, and cannot tolerate oral or enteral feeding. Provision of calories by lipids, reduces the amount of glucose that would otherwise be necessary to supply calories in a 24 hour period. Dextrose, a form of glucose, can be used to make intravenous preparations. Administration of high dextrose loads contributes to hyperglycemia in critically ill patients, and has been associated with higher risk for morbidity/mortality². Lipid emulsions are also intended to supply patients with essential fatty acids.

Previous approvals of lipid injectable emulsions were largely premised on the fact that the products provided a known amount of calories based on the amount of fat present and that they served as a source of essential fatty acids. Lipids in the form of triglycerides can be converted into energy, carbon dioxide, and water in the mitochondria via the β -oxidation process and citric acid cycle, thus comprising one of the basic nutritional requirements of mammalian metabolism in addition to glucose, amino acids, and electrolytes.³ It is also a well-established scientific fact that fatty acids in the form of triglycerides are major sources of dietary energy and are more calorie-dense than protein and dextrose.⁴ Because the energy value of fatty acids depends on the length of the carbon chain, long chain fatty acids (provided by soybean, olive and fish oil) provide 9kcal/g while MCTs provide 7kcal/g.⁵ They also provide the structural components of cell membranes, contribute to membrane fluidity, are the precursors of biological mediators, and are regulators of gene expression.

Intralipid (NDA 017643) was the first intravenous lipid emulsion product approved in the U.S. in 1975. Intralipid contains one active ingredient, soybean oil. The original approval

² Olveira G, et al. Diabetes Care. May 2013, Vol 36 no. 5: 1061-1066.

³ Berg J.M., Tymoczko J.L., Stryer L., Biochemistry, 5th edition, New York: W H Freeman; 2002 (See Chapter 17, Citric Acid Cycle).

⁴ Berg, Chapter 22.

⁵ Berg, Chapter 22.

contained 10% soybean oil (NDA 017643), and subsequently in 1981 the 20% emulsion was approved (NDA 18449). Intralipid 10% is rarely used because of the adverse events related to the higher concentrations of free phospholipid, which interferes with the lipoprotein lipase activity. Both concentrations are approved for use in adult and pediatric patients.

The following table provides for background purposes the approval history of currently active NDAs, and a description of the composition of the lipid emulsion according to the (b) (4) oils used in their manufacture. All have a similar labeled indication to the one proposed for Smoflipid. Only Intralipid and Nutrilipid are approved for use in both pediatric patients and adults.

Active Ingredients for Smoflipid and Currently Approved and US-Marketed Intravenous Lipid Formulations

Brand Name <i>(approval date)</i> <i>(Sponsor)</i>	Soybean Oil	Olive Oil	Medium Chain triglycerides	Fish Oil
Smoflipid (20%) <i>(FK)</i>	(b) (4)			
Intralipid (10%, 20% 30%*) <i>(1975,1981,1993)</i> <i>(FK)</i>	(b) (4)	NA	NA	NA
Nutrilipid (10%, 20%) <i>(1993)</i> <i>(BBraun)</i>	(b) (4)	NA	NA	NA
Clinolipid <i>(2013)</i> <i>(Baxter)</i>	(b) (4)	(b) (4)	NA	NA
Kabiven, Perikabiven** <i>(2014)</i> <i>(FK)</i>	(b) (4)	NA	NA	NA

**Intralipid 30% (NDA 019942) is not intended for direct intravenous administration; rather it is to be diluted to either 10 or 20% concentrations for infusion.*

** *Kabiven, Perikabiven also include amino acids, glucose and electrolytes.*

The lipid injectable emulsion products containing safflower oil that were initially approved in the U.S. have been withdrawn from the market. Liposyn I ((b) (4) safflower oil) was reportedly discontinued by the sponsor due to concerns about its low alpha-linolenic acid (ALA) content and the predisposition of patients to have neurological adverse events as a consequence of essential fatty acid deficiency (EFAD). Liposyn II ((b) (4) safflower oil and (b) (4) soybean oil) was reportedly discontinued by the sponsor due to the inability to acquire safflower oil and Liposyn III ((b) (4) soybean oil) was reportedly discontinued by the sponsor for reasons not related to safety.

Essential fatty acids

Lipid emulsions also provide the essential fatty acids (fatty acids cannot be synthesized by the human body):linoleic acid (LA) and alpha-linolenic acid (ALA). Intralipid contains high

concentrations of essential long-chain fatty acids; linoleic acid (LA) and alpha-linolenic acid (ALA). These essential fatty acids cannot be synthesized de novo. Essential fatty acids are necessary for a variety of physiological functions, including structural components of cell membranes and tissues, secondary messengers and mediators, as well as providing sources of energy in the form of triglycerides.

The following tables display the essential fatty acids provided by Intralipid and a complete profile of Smoflipid based upon chemical specifications.

Currently Approved Products - Active Ingredients

FATTY ACIDS	INTRALIPID 20% ((b) (4) soybean oil)
Linoleic acid * (LA) (n-6)	range (b) (4) mg/mL
α-Linolenic acid * (ALA) (n-3)	range (b) (4) mg/mL

Smoflipid Specifications

Fatty Acid	Oil Type (active ingredient)	% of Oil in SMOFIipid	Mean concentration* Based on DS specification mg/mL	Limit in SMOFIipid Range mg/mL
Caprylic acid (C8)				(b) (4)
Capric acid (C10)				
Oleic acid (C18:1)				
Linoleic * (C18:2)				
Alpha-Linolenic * (C18:3)				
Eicosapentenoic acid (C20) EPA				
Docosahexaenoic acid (C22) DHA				

**essential fatty acids*

E.g.: Concentration = Amount (b) (4)
(20% SMOFIipid drug product).*

Note from the table above (b) (4)

Although the types of studies utilized to support efficacy are small and descriptive in nature, they are adequate and well-controlled, and together with generally accepted scientific

knowledge, support a finding of substantial evidence of effectiveness for the proposed indication; and they also provide supportive clinical information regarding the safety of Smoflipid. One important efficacy/safety issue is essential fatty acid deficiency (EFAD) which is more readily apparent and severe in neonates compared to adults. In adults, essential fatty acid deficiency may develop over a long period of time and results in reversible dermatologic changes. Pediatric patients develop EFAD more rapidly, and develop serious clinical signs and symptoms related to deficiencies in neurologic growth and development. These changes may not be reversible. Therefore, additional safety information with longer exposure to Smoflipid is necessary to evaluate the safety in neonatal and young pediatric patients.

The Holman index has been used as a chemical marker to evaluate the adequacy of the provision of LA and ALA. The evaluation of EFAD has relied upon the measurement of mead acid (a triene) and arachidonic acid (a tetraene) in plasma or red blood cell samples. The “Holman index” is then obtained by dividing the quantity of mead acid by that of arachidonic acid. It is based on the observation that the same enzymes responsible for converting linoleic (LA) acid and alpha-linolenic (ALA) acid into arachidonic acid and eicosapentaenoic acid (EPA) also convert oleic acid into mead acid if LA and/or ALA are less available. Based on studies by Holman et.al (1979), levels greater than 0.2 represent chemical EFAD as clinical symptoms may lag behind these measurements^{6,7}. The medical reviewer points out that “Since the Holman index was developed several decades ago, there have been clinical analytical method advancements that have led to discussion about the appropriate ranges for the triene/tetraene ratio (Lagerstedt 2001). The Mayo Medical Laboratories have established reference ranges for the triene/tetraene ratio that are very different from the classic Holman index. Further discussions are needed to determine the most appropriate measurements and reference values to diagnose EFAD”⁸.

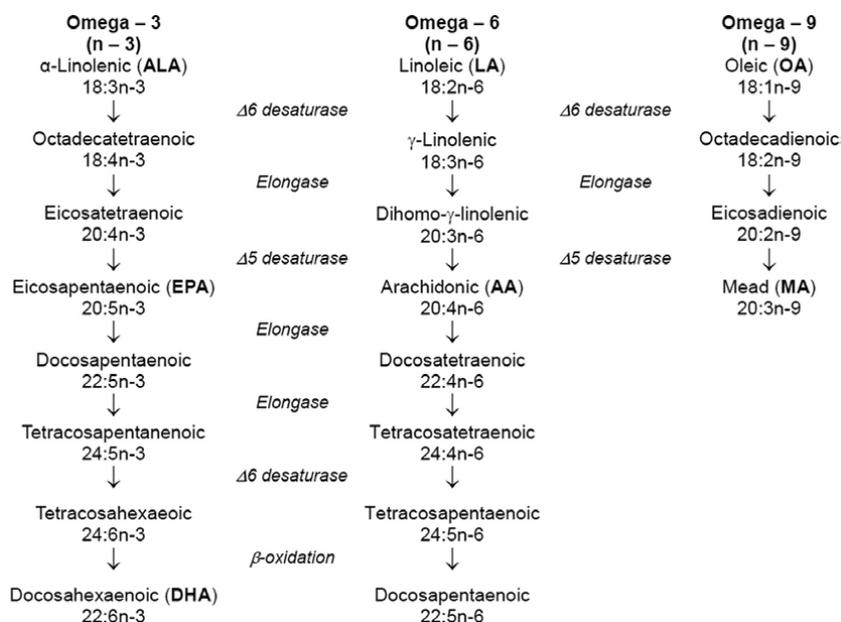
The applicant justifies this novel fat emulsion as supplying enough essential FA for adults and pediatric patients based on composition calculations. They further have stated that the supply of EPA and docosahexaenoic acid (DHA) which are found in Smoflipid would not be adequately evaluated utilizing the Holman index because they do not directly influence the generation of mead acid. EPA and DHA are derived from essential fatty acids, and the applicant states that this may be beneficial in preventing EFAD. The applicant also notes that “the intake of EPA and DHA in addition to the intake of LA and ALA must be considered to determine whether adequate essential fatty acids are provided, and the Holman index must not be the only parameter used to evaluate the essential fatty acid status of the patients”. In our review we analyzed the measurements of ALA and LA as well as the Holman index in patients taking Smoflipid compared to the (b) (4) soybean oil comparators (see Pediatric efficacy and safety sections).

⁶ Holman RT, Smythe L and Johnson S. Effect of sex and age on fatty acid composition of human serum lipids. *Am J Clin Nutr.* 1979;32:2390-9.

⁷ Hamilton C, Austin T, Seidner DL. Essential fatty acid deficiency in human adults during parenteral nutrition. *Nutrition in Clinical Practice* 2006; 21(4):387-94.

⁸ Lagerstedt S, Hinrichs D, Batt S, Magera M, Rinaldo P, McConnell J. Quantitative determination of plasma C8-C26 total fatty acids for the biochemical diagnosis of nutritional and metabolic disorders. *Molecular Genetics and Metabolism* 2001; 73:38-45.

Desaturation and Elongation of Alpha-Linolenic Acid, Linoleic Acid and Oleic Acid to Docosahexaenoic Acid, Docosapentaenoic Acid, and Mead Acid⁹.



Parenteral Nutrition Associated Liver Disease and Phytosterols

Phytosterols are an impurity present in all lipid emulsion products derived from plant oils. Phytosterols that are poorly absorbed by the gut when ingested orally (estimated 5% bioavailability) are expected to far exceed the exposure achieved in a normal human diet when administered intravenously. Phytosterols have been linked to the development of parenteral nutrition associated liver disease (PNALD)¹⁰. PNALD is believed to occur in stages starting with parenteral nutrition associated cholestasis (PNAC) as the predominant presentation in infants. As PNAC progresses to PNALD, the process can lead to a high incidence of morbidity and mortality¹¹. Previously, the division had determined that it is important to test intravenous lipid emulsion products with validated assays and establish limits for the presence of individual component phytosterols. The same applies to this product. The studies presented and reviewed in this application are too short in duration to evaluate the risk of developing parenteral nutrition associated liver disease. Because the risk of development of PN-related liver disease is highest in pediatric patients, especially neonates, a post-market required (PMR) trial to address this question will enroll this young population. However, in order to assure the safety of the children enrolled in the trial, the PMR trial to assess the risk of development of EFAD in children must be complete before initiation of this trial. The applicant will be required to incorporate a phytosterol depleted Smoflipid product for evaluation in this PMR

⁹ Kalish BT, Fallon EM and Puder M. A tutorial on fatty acid biology. J Parenter Enteral Nutr. 2012;36:380-8.

¹⁰ Xu Z, and Li Y-S. Pathogenesis and treatment of parenteral nutrition-associated liver disease. Hepatobiliary Pancreatic Dis Int. Vol 11, No 6. December 15, 2012.

¹¹ Rangel SJ, et al. Parenteral nutrition-associated cholestasis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg. 2012 Jan;47(1):225-40. doi: 10.1016/j.jpedsurg.2011.10.007.

trial. The PMRs related to this potential safety issue are listed below (SECTION 8: Safety: Pediatric Trials).

Elemental impurities

Because of the concern regarding the potential of exposure to high levels of elemental impurities due to the chronic administration of large volume parenteral products, a class PMR regarding measuring and ensuring adequate control of these impurities, especially the heavy metals, was established for the marketed products. It required that the following metal impurities be addressed: [REDACTED] (b) (4)

[REDACTED] The applicant was aware of this and has submitted appropriate information for review to this application.

The proposed Smoflipid formulation was first approved in Sweden in 2004 in adults and pediatric patients (neonates, infants and children), and is approved in the EU and non-EU countries. In 2009 the EU approved it for use in pediatric patients. It is approved in Canada for adult patients.

Regulatory

3. CMC

Smoflipid contains 4 active ingredients, soybean oil (USP), olive oil (NF), medium chain triglycerides (NF) and fish oil (USP, Dietary Supplement). The currently marketed US injectable lipid emulsion products are composed of either soybean oil alone or a combination of two active ingredients, soybean oil and olive oil.

Drug substance

Smoflipid is a 20% emulsion and 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 [REDACTED] (b) (4)

[REDACTED] 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 obtained from another supplier under a DMF [REDACTED] (b) (4). The DMF is deemed adequate by the reviewers.

Drug products

Smoflipid is a sterile parenteral nutrition product intended for intravenous administration 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- α -tocopherol, purified egg phospholipids, glycerol, and sodium oleate. The 9 major components of the fatty acids in Smoflipid are oleic acid (23% to 35%), linoleic acid (14% to 25%), caprylic acid (13% to 24%), palmitic acid (7% to 12%), capric acid (5% to 15%), stearic acid (1.5% to 4%), α -linolenic acid (1.5% to 3.5%), eicosapentaenoic acid (EPA; 1% to 3.5%), and docosahexaenoic acid (DHA; 1% to 3.5%).

The product is packaged in 3 sizes: 100 mL, 250 ml and 500 mL in a one chamber bag made of (b) (4). It is approved for use with other LVP products. The potential migrants in the container and closure system were evaluated for toxicity by the preclinical pharmacology-toxicology group and were deemed acceptable (see non-clinical section).

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 by the reviewers.

The CMC review states that “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”.

The applicant has provided details of assay methods for quantitative determination of phytosterols; (b) (4). Further analysis of the presence of phytosterols will be performed in post-marketing required studies described below.

The CMC review of the applicant’s proposed limits for each of the elements listed above was based upon a verification of the applicant’s calculations by FDA (based upon the ICH Q3D, option 3 equations), and the calculations were in agreement. They concluded that based upon the ICH equation and taking into consideration the ICH limits and maximum daily dose, the proposed limits are deemed adequate. The ICH Q3D also recommends that the metals (b) (4) be addressed. The reviewer stated that given the manufacturing process, it is not expected that these elements would be present in the product. Measurements of the nine elemental impurities in three batches of Smoflipid at 12 months were well within the limits set. While the (b) (4) specifications were deemed appropriate by the OPQ reviewer, however, (b) (4) upon further review by the nonclinical toxicology group it was recommended to change the specifications. The applicant submitted the updated specification and OPQ found that acceptable and recommended approval of the new (b) (4) impurity specification.

The product quality microbiology reviewer recommended approval. This product is (b) (4).

Based on the CMC –ONDP review the following conclusions were reached regarding approvability:

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

On October 6, 2015, the Office of Process and Facility has issued an overall “Approval” recommendation for the facilities involved. (Attachment 1)

Label/labeling issues have been satisfactorily resolved (Attachment 2).
Therefore, from the OPQ perspective, this NDA is recommended for Approval.”

I concur with the conclusions reached by the OPQ chemistry and microbiology reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology program consists of safety pharmacology, repeat dose IV toxicity in two mammalian species (rat and dog), and genotoxicity studies conducted with Smoflipid, with support from nonclinical studies conducted by Fresenius on its other lipid-containing products.

The following is a summary from the Nonclinical Pharmacology/Toxicology review.

“The applicant has provided adequate nonclinical pharmacology and toxicology information in support of the NDA application. Nonclinical studies submitted are with Smoflipid or its constituent lipids: long chain triglycerides (LCT), medium chain triglycerides (MCT) and omega 3 (n-3) fatty acids (Omegaven) and Intralipid (soybean oil emulsion). In nonclinical studies, Smoflipid or its constituent fatty acids were generally well-tolerated in a rodent (rats) and a non-rodent (dogs) species at the maximum doses administered, with slight or moderate, but reversible adverse effects. The safety of Smoflipid and/or the individual lipid constituent, soybean oil (Lipovenos 20%, Intralipid 20%), fish oil (Omegaven 10%) has been established in safety pharmacology, repeat dose IV toxicity and genotoxicity studies. There are no significant nonclinical safety concerns for Smoflipid 20 %.”

“In repeat-dose toxicity studies with Smoflipid 20 % in rats, it was tolerated for only up to 4 weeks. Administration of Smoflipid beyond 4 weeks at the highest dose of 18g/kg/day (3.8 mL/kg/hr) was associated with mortalities and a wide range of toxicities, related to the continuous 24 hour infusion of a large volume of the fat emulsion. In dogs, infusion of Smoflipid 20% (6 hr/day) for 13 weeks was well-tolerated with limited adverse effects, related to the nature of the formulation and administration of a large volume of the parenteral emulsion. There were no mortalities in dogs, and no changes in hemodynamic or ECG parameters were observed. Mild to moderate indurations observed at the infusion site, and slight discoloration and fatty changes in the liver were fully or partially reversible at the end of the 4-week recovery period. The other components of Smoflipid were similarly well-tolerated in rodents and non-rodents following repeated administration for up to 13 weeks.” Additional safety pharmacology studies on Smoflipid were not needed because these repeat-dose chronic

toxicity studies in two animal models adequately established the absence of any adverse effects on any organ system or function.

“Smoflipid and/or its constituents were not genotoxic in a standard battery of genotoxicity assays. Reproductive toxicology studies were not performed with Smoflipid. However, in a pre- and post-natal developmental study in rabbits with Intralipid, no teratogenic effects, or effects on fetal development were observed.”¹²

“For the intended indication . . . conventional carcinogenicity studies are generally not required since treatment [with parenteral lipid emulsion products] implies supplementation at levels only high enough to satisfy the major part of the energy requirement and to protect from essential fatty acid deficiency.” In other words, carcinogenicity studies would not be expected to yield useful data because exposure would not be expected to exceed levels beyond those resulting from ordinary dietary intake.¹³

“The safety assessments of the potential migration of component materials of the (b) (4) packaging system into the Smoflipid 20 % emulsion parenteral infusion product and the associated risk for the recipient patients were evaluated. In the safety assessment of the potential migrants (leachables and extractables), there was a separation or clear separation between calculated patient exposures and the permitted daily exposure (PDE) as calculated according to animal or human toxicity data from toxicological information or as calculated according to the ICH Q3C(R5) guidance.”

“The safety assessment of the potential leachables/extractables appears to be adequate and acceptable, and does not raise any safety concerns. In addition, there are no safety concerns with potential and established migrants from (b) (4) the storage of the raw material oils used in the synthesis of Smoflipid.”

The nonclinical pharmacology/toxicology reviewers recommended approval.¹⁴

¹² Lipid emulsions are not expected to have embryotoxic or teratogenic effect, when given in recommended doses as substitution therapy. Further, nonclinical reproductive toxicology studies for this product would likely be infeasible given the inability of the animal model to sustain the IV infusion of the large volume of lipid emulsion over several weeks. Even if such studies were feasible, the interpretation of such data would likely be difficult due to adverse effects related to the IV infusion of the large volume of lipid emulsion.

¹³ In addition, carcinogenicity studies, which are typically conducted over a period of 2 years in rodents, would likely be unfeasible given the inability of the animal model to sustain the IV infusion of the large volume of lipid emulsion over such a time frame.

¹⁴ No other pharmacology or toxicology studies using Smoflipid were needed for approval. For example, primary pharmacodynamics studies would likely not be useful as there is no therapeutic target; glucose, amino acids, fatty acids, and electrolytes comprise the basic nutritional requirements of mammalian metabolism. Secondary pharmacodynamic studies are not feasible (or relevant) for lipid injectable emulsions because these products lack a specific site of action. ADME (absorption, distribution, metabolism, and excretion) studies are not needed because the metabolites of the parenteral lipid emulsion product are endogenously present in the body; in addition, this product is 100% bioavailable and thus its conversion to into energy can readily be calculated without such studies.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/toxicology issues that preclude approval. I also note that although the pharmacology/toxicology reviewers refer in their review to literature or studies of all lipid classes, upon further consultation with them it is not necessary to rely on literature or on studies not conducted by the sponsor to support approval of this product.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology/biopharmaceutics reviewers stated that they reviewed the results of two clinical pharmacology studies which were submitted in support of this NDA; however, both studies were considered to be exploratory. The constituents of Smoflipid 20% used in these two studies were different from the current proposed product. These studies were conducted with 10 to 12 healthy subjects each given single short term (4 to 6 hours) infusion and dated from 19 years ago. In addition, the bioanalytical methods were not described in detail and method validation results were not provided. As a consequence, the information is of limited value and will not be included in labeling. Because these studies are not necessary for the NDA approval, the weaknesses of these study reports was not considered a refuse-to-file issue or approval issue. Clinical pharmacology studies generally assess rate and extent of exposure to the therapeutic moiety. the product is 100% bioavailable, and given the indication, i.e., source of calories and essential fatty acids, the rate and extent of exposure to particular moieties would not be particularly informative with respect to this indication.

The reviewers agreed to the inclusion of the potential interaction of Smoflipid with coumarin and coumarin derivatives in section 7 of the professional labeling (Drug Interactions), because soybean oil and olive oil naturally contain vitamin K₁.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

This section is not applicable because the product is not intended to have antibiotic treatment effects.

7. Clinical/Statistical-Efficacy

The applicant's phase 3 development program was the basis of the submission. The applicant submitted the results of 10 studies and clinical trials. Two studies were small clinical pharmacology studies, 5 clinical trials were in adults and 3 were in pediatric patients. Details of these studies are described below (note one additional clinical trial in adults was performed in China and is not part of this review for efficacy). No formal statistical review was conducted. The statistical reviewer stated in his filing review,

“The submitted study results should be considered descriptive or observational only as they do not rely on appropriate inferential statistics or trial designs that would be considered adequate to support specific endpoint testing. At the time of filing, we

considered this application as ‘No Action Indicated’. The statistical reviewer will, however, be available to the clinical review team, as needed, to address specific questions or concerns that would require statistical response”.

Given the nature of the indication in that it does not include clinical outcomes but rather the drug is intended for use as a source of calories and essential fatty acids, specific clinical endpoints evaluated by formal statistical analyses are not needed to support approval.

Adult Clinical Trials:

The objectives and designs of the six major randomized adult studies are listed below in a table reproduced from the medical officer clinical review.

Trial (Trial Time Period)	Trial Design	Dosing	Number of patients randomized/treated	Study population	Planned Duration
FE-SM-03-DE (09/1997-07/1998)	Phase 3, double-blind, randomized, active-controlled, parallel-group, multicenter	<u>SMOflipid 20%</u> central IV infusion of 1.5 g/kg/d <u>Lipovenös 20%*</u> central IV infusion of 1.5 g/kg/d	249/249 SMOF 20%: 126 Lipovenös 20%: 123	Male and female adult patients (aged 18 years or older) following major abdominal, thoracic, or urological surgery	Continuous infusion over approximately 24 hours per day for 5 days after surgery
FE-SM-04-CH (01/1998-08/1998)	Phase 3, double-blind, randomized, active-controlled, parallel-group, single-center study	<u>SMOF 20%</u> central IV infusion up to a maximum of 2 g/kg/d <u>Lipovenös 20%</u> central IV infusion up to a maximum of 2 g/kg/d	35/32 SMOF 20%: 16 Lipovenös 20%: 16	Male and female adult patients (aged 18 years or older) in need of TPN	Continuous infusion over 18 to 24 hours per day for 10 to 14 days
03-3CB7-001 (07/2004-02/2005)	Phase 3, prospective, open-label, randomized, active-controlled, parallel-group, single-center study	<u>SmofKabiven</u> central IV infusion of 15-30 mL/kg/d, corresponding to 0.57-1.14 g/kg/d (SMOflipid 20%) <u>Kabiven</u> central IV infusion of 15-30 mL/kg/d, corresponding to 0.6-1.2 g/kg/d (Intralipid 20%)	60/53 SmofKabiven: 26 Kabiven: 27	Male and female adult patients (aged 18 to 85 years) following major intestinal tract surgery requiring PN	Continuous infusion for approximately 24 hours per day for 5-7 days after surgery
03-3CB8-001 (07/2004-10/2005)	Phase 3, prospective, open-label, randomized, active-controlled, parallel-group, multicenter study	SmofKabiven Peripheral peripheral IV infusion, MXDD: 40 mL/kg/d, corresponding to 1.13 g/kg/d (SMOflipid 20%) Kabiven Peripheral peripheral IV	52/52 SmofKabiven Peripheral: 27 Kabiven Peripheral: 25	Male and female patients (aged 18 to 85 years) requiring PN	Peripheral IV infusion for 14-24 hours per day for 5-7 days

Trial (Trial Time Period)	Trial Design	Dosing	Number of patients randomized/treated	Study population	Planned Duration
		infusion, MXDD: 40 mL/kg/d, corresponding to 1.42 g/kg/d (Intralipid 20%)			
05-SMOF-006 (10/2007-10/2008)	Phase 3, double-blind, randomized, active-controlled, parallel-group, multicenter	SMOFlipid 20% central IV infusion of 1-2 g/kg/d Intralipid 20% central IV infusion of 1-2 g/kg/d	75/73 SMOF 20%: 34 Intralipid 20%: 39	Male and female adult patients (aged 18 to 85 years) in need of PN	Continuous infusion over 10-24 hours per day for 5-7 days per week for 4 weeks
**SMOF-001-CP3 (08/2008-09/2009)	Phase 3, double-blind, randomized, active-controlled, parallel-group, multicenter	Smoflipid 20% - 1.2 g/kg/d Intralipid 20% - 1.2 g/kg/d	212/212 SMOFlipid:: 106 Intralipid: 106:	Male and female adult patients (aged 18 to 80 years) after moderate and major abdominal surgery	Central or peripheral infusion for 6 days

* Lipovenös (a Fresenius product) is a 20% lipid emulsion containing (b) (4) soybean oil. Although not approved in the United States, it is approved in other jurisdictions like the European Union (EU).

** Data from Trial SMOF-001-CP3 was not included in the Integrated Summary of Safety (ISS) or Integrated Summary of Efficacy (ISE)

Of the studies listed above, the medical officer’s clinical review relied on the evidence from the three double blind, randomized, active controlled trials. The largest of these studies enrolling 249 post-operative patients (FE-SM-03-DE) had a 5 day treatment period. Study FE-SM-04-CH enrolled 35 patients who were treated for from 10 to 14 days. The third study, 05-SMOF-006, treated patients for the longest duration, 28 days, and enrolled 73 patients. The last two double-blind randomized, active controlled trials enrolled patients who were in “need” of parenteral nutrition. Although these studies were not powered to demonstrate “clinical efficacy” regarding other claims initially sought by the sponsor (e.g., clinical superiority or non-inferiority claims), they collected data relevant to the efficacy review of this NDA and are relied upon as evidence for the proposed indication for which approval will be granted. In the adult studies included in this submission, the applicant states that only study FE-SM-03-DE was designed to examine changes in triglyceride levels as the primary efficacy endpoint; while the other clinical studies in adult patients evaluated triglyceride levels and other potential measurements of nutritional status or lipid metabolism as assessments of safety. In order to review other secondary indicators of nutrition to support efficacy for the proposed indication, the clinical reviewer also examined the various metrics of nutrition such as albumin, prealbumin, nitrogen balance, antropometrics, essential fatty acids, triglycerides and fatty acid across the various trials.

- Study FE-SM-03-DE was conducted in 249 postoperative adult patients in need of total parenteral nutrition (TPN) for ≥ 5 days. The objective of the study was to evaluate efficacy, safety, and tolerance of SMOFlipid 20% compared to Lipovenös® 20% (soybean oil emulsion). Efficacy was assessed on the basis of effects on serum triglyceride concentrations, fatty acid profiles as well as fatty acids in plasma and cell membrane phospholipids (defined as primary and secondary efficacy variables in the clinical study report [CSR]), and albumin levels (defined as a safety variable in the CSR). From baseline to Day 6, mean triglyceride levels increased similarly in both the Smoflipid and comparator groups. A clinical outcome monitored in this study was length of stay in hospital and ICU. The mean length of stay in the hospital and ICU was similar for the two treatment groups (based upon descriptive statistics).
- Study FE-SM-04-CH treated 32 adult patients in need of TPN for 10 to 14 days. The objective of the study was to evaluate safety and tolerance of SMOFlipid 20% compared to Lipovenös 20%. Efficacy was assessed on the basis of effects on serum triglyceride concentrations (defined as a safety variable in the CSR). Patients were treated with either Smoflipid or a soybean oil lipid emulsion. The increase in mean triglyceride levels from baseline to the final assessment was similar in both the Smoflipid and comparator groups.
- 05-SMOF-006 enrolled 75 and treated 73 adult patients in need of PN for at least 4 weeks. The primary objective of the study was to compare safety and tolerance of SMOFlipid 20% with Intralipid® 20%. Efficacy was assessed on the basis of effects on serum triglyceride levels, fatty acids in plasma lipoproteins and red blood cell (RBC) phospholipids, and albumin levels (all defined as safety variables in the CSR). Changes in mean triglyceride levels from baseline values to Week 4 were similar in both the Smoflipid and comparator groups. Mean albumin levels demonstrated a comparable decrease in both groups. Mean changes in body weight (kg) and BMI (kg/m²) were similar in both the Smoflipid and comparator group. In a subset of 33 patients fatty acids were evaluated. Fatty acid profiles were consistent with the composition of the lipid emulsion. Smoflipid 20% was associated with lower mean concentrations of the essential fatty acid linoleic acid compared with soybean oil based comparators and an increase in omega 3 fatty acids when compared with soybean oil based products. There was limited data reported on the triene:tetraene ratio.

In summary, none of the submitted trials were adequately designed and/or powered to establish nutritional equivalence or superiority of Smoflipid to the currently marketed lipid emulsion products. No study established that Smoflipid is superior or non-inferior to available therapy on a clinical outcome measure. While the applicant designed Study FE-SM-03-DE as a non-inferiority study regarding serum triglyceride measurements, neither superiority nor non-inferiority was demonstrated. However, the applicant's full proposed indication is "Smoflipid is indicated in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated." No clinical outcome claims were included in the proposed indication. The failure to establish superior or non-inferior efficacy in the trials submitted to support this NDA is not an approval issue. Smoflipid provides a source of calories and essential fatty acids for patients requiring

parenteral nutrition. These trials, together with generally accepted scientific knowledge, support a finding of substantial evidence of effectiveness for the proposed indication. As an injectable lipid emulsion, Smoflipid provides the purported nutritional support which is self-evident by assessing the product's component contents. The product is intravenously infused, and the amount of calories provided can be simply determined based on the amount of lipids contained in the product, since it is well established: long chain fatty acids (provided by soybean, olive and fish oil) provide 9kcal/g while MCTs provide 7kcal/g.¹⁵ The three studies described above are adequate and well-controlled and support Smoflipid's clinical effect on nutrition by measuring other variables such as triglyceride levels, fatty acid profiles and serum concentrations of albumin.

The applicant proposed adult dosing instructions for the product label, which were consistent with the sponsor's Intralipid 20% labeled dose instructions. With regard to the proposed dosing for Smoflipid, I also note that the labeled dose is in agreement with the ASPEN guidelines¹⁶ although it is not necessary to rely on those guidelines for approval of the dosing regimen. The ASPEN guidelines state that adult energy requirements range from 20-30 kcal/kg, and that 15-30% of the calories should be provided as fat. Additionally, the ASPEN guidelines state that "there is limited clinical benefit when fat content exceeds 30% of non-protein calories," which results in recommendations that the fat content of parenteral nutrition formulations should not exceed 2.5 g/kg/day.

As noted above, Smoflipid contains essential fatty acids linoleic acid (LA) and alpha linolenic acid (ALA). Smoflipid contains (b) (4) omega-6 fatty acids (b) (4)

(b) (4) There are limited data available upon which to make firm recommendations. The applicant concluded that the LA intake in adults should range from (b) (4)% of total energy intake and the ALA intake should range from (b) (4)% of total daily energy intake. Based upon the calculations by the applicant using data based on the formulation and dosing instructions and confirmed by the medical review, the calculated volume of Smoflipid required in adults to provide the EFAs is less than the total volume that would be delivered to achieve the fat calories needed to meet energy requirements in adults based upon the labeled dosing. The reviewers were reassured; however, there remain concerns regarding the actual EFA requirements, especially in young children and the limitation of the measures used to assess plasma EFA levels. No evidence of EFAD was seen in the adult trials; however, the duration of these studies may not have been long enough to detect the clinical manifestations.

The clinical review concluded that "Smoflipid appears to be a safe and effective source of calories and essential fatty acids in adult patients who require parenteral nutrition." I concur

¹⁵ All classes of fatty acids can be converted into energy, carbon dioxide, and water in the mitochondria via β -oxidation and citric acid cycle, thus comprising one of the basic nutritional requirements of mammalian metabolism in addition to glucose, amino acids, and electrolytes. Berg J.M., Tymoczko J.L., Stryer L., Biochemistry, 5th edition, New York: W H Freeman; 2002 (See Chapter 17, Citric Acid Cycle). It is also a well-established scientific fact that fatty acids in the form of triglycerides are major sources of dietary energy and are more calorie-dense than protein and dextrose. (Berg, Chapter 22). Because the energy value of fatty acids depends on the length of the carbon chain, long chain fatty acids (provided by soybean, olive and fish oil) provide 9kcal/g while MCTs provide 7kcal/g. (Berg, Chapter 22).

¹⁶ Task Force for the Revision of Safe Practices for Parenteral Nutrition. JPEN, J Paenteral Enteral Nutr 2004, 28:S39, PMID:15568296

with the medical reviewer findings regarding provision of energy in adults; and I find that Smoflipid is effective for such use. The product does contain essential fatty acids (EFA); however, there are concerns about the adequacy of the amounts of essential fatty acids it provides, particularly for children. In adults essential fatty acid deficiency (EFAD) manifestations are dermatological and are reversible with supplementation, in children the neurological impact of EFAD could have permanent developmental consequences. This will be discussed in the following pediatric clinical trials section and in Safety Section 8.

Pediatric Clinical Trials:

The objectives and designs of the three major randomized pediatric studies are listed below in a table reproduced from the medical officer clinical review.

Trial (Trial Time Period)	Trial Design	Dosing	Number of patients randomized/treated	Study population	Planned Duration
00-SMOF-002 (05/2003-05/2005)	Phase 2b, double-blind, randomized, active-controlled, parallel-group, single-center	SMOFlipid 20% central IV infusion approximately 2 g/kg/d Intralipid 20% central IV infusion approximately 2 g /kg/d	28/28 SMOF 20%: 15 Intralipid 20%: 13	Male and female infants and children (aged 1 month to 11 years) with stable disease requiring PN	1 week run-in period with Intralipid 20%; 1 day washout; SMOFlipid 20% or Intralipid 20% as 12-14 hours continuous infusion per day for 4-5 days per week for 4 weeks
00-SMOF-004 (04/2003-02/2006)	Phase 2b, double-blind, randomized, active-controlled, parallel-group, single-center	SMOFlipid 20% or Intralipid 20% IV via umbilical artery or peripheral infusion Dose (in g/kg/d): Day 1: 0.5 Day 2: 1.0 Day 3: 1.5 Days 4-14: 2.0	60/60 SMOF 20%: 30 Intralipid 20%: 30	Male and female premature neonates (gestational age <34 weeks; 0 to 7 days old) with birth weight of 1000 to 2500 g and requiring PN	Continuous infusion for 20-24 hours per day for 7 to 14 days
03-SMOF-005 (05/2004-02/2006)	Phase 3, double-blind, randomized, active-controlled, parallel-group, 2-center	SMOFlipid 20% or Intralipid 20% IV via peripheral indwelling cannula or central infusion Dose (in g/kg birth weight/d): Days 1-3: 1.0 Day 4: 2.0 Day 5: 3.0	84/84 SMOF 20%: 42 Intralipid 20%: 42	Male and female premature neonates (gestational age <34 weeks; 0 to 7 days old)c with birth weight of 500 to 2000 g and requiring PN	Continuous infusion for 18-24 hours per day for 7 to 14 days

Trial (Trial Time Period)	Trial Design	Dosing	Number of patients randomized/treated	Study population	Planned Duration
		Days 6-14: 3.5			

The review relied on the evidence from the three double blind, randomized, active controlled trials listed above.

For all three studies, the active comparator was the approved soybean oil-based lipid emulsion, Intralipid 20%. The primary objective of the studies was to evaluate the safety and tolerability of Smoflipid compared to Intralipid in the enrolled populations. The secondary objective was to look at efficacy.

In the first study (00-SMOF-002), 15 patients received Smoflipid (7 patients were less than 2 years of age) and 13 pediatric patients received Intralipid (6 patients were less than 2 years of age). The 27 day duration of study treatment was the same in both treatment groups. The study ultimately enrolled younger patients in the Smoflipid group, with 5 of the 7 patients under 1 years of age in the Smoflipid group and only 3 of 6 under one year of age in the Intralipid group. (b) (4)

As pointed out by the DPMH reviewer “pediatric patients in the study were allowed up to 50% of their intake from enteral sources. Only 18% of patients were dependent on parenteral nutrition as their sole source of calories. Additionally, patients were only treated up to 27 days which may not have been long enough to detect EFAD. Consequently, the inclusion of enteral feedings and study duration may have decreased the ability to detect EFAD in this patient population.” None of the patients in the study developed EFAD.

In the second study (00-SMOF-004), 60 premature infants were stratified according body weight (1000 – 1499 grams, 1500 – 1999 grams and 2000 – 2500 grams) and treatment group (Smoflipid vs. Intralipid), for a total of 10 patients per group. All patients were less than 34 weeks gestation and were treated for 7 to 14 days. Safety variables included measures of serum triglycerides, liver enzymes, cholesterol and monitoring for AEs. Efficacy variables included change in body weight between day 1 and day 8, C-reactive protein level, sepsis score, days with antibiotic therapy, the use of mechanical ventilation or oxygen therapy, change in length during the treatment period and evaluation of the fatty acid pattern in erythrocytes, phospholipids, alpha-tocopherol and lipid peroxidation in plasma. Not all patients were treated for 14 days, with a mean treatment period of 12 days in the Smoflipid group and 9 days in the Intralipid group. (b) (4)

(b) (4)

It should be noted that the percentage of patients receiving enteral feeding and the relatively short duration of the study may have limited the ability to detect EFAD in this patient population.

The third study (00-SMOF-005) also enrolled premature infants, but enrolled patients with a birth weight as low as 500 grams and stratified according to birth weight (500 – 1000, 1001 – 1500 grams and 1501 – 2000 grams) and treatment group (Smoflipid vs. Intralipid). The study included 84 patients, 42 in each treatment group with 25/30/29 per weight range; patients were treated for 7 to 14 days with an average of 8.2 days for Smoflipid and 8.6 days for Intralipid over the complete study period. There were 2 centers that enrolled patients in the study. Center 1 did not comply with the protocol and calculated fat intake as the sum of parenteral and enteral feeding. Additionally, at center 1, dosing was triggered by the day of life and not study day as required by the protocol. These protocol violations led to a lower intake of study medication in both treatment groups at the center. At center 2, dosages were in compliance with the protocol. As a result, the efficacy analyses were based on the 52 patients enrolled at center 2 and not the total study population of 84 patients. The primary study endpoint was measure of serum triglycerides (b) (4)

(b) (4)

(b) (4)

DPMH agrees with the Division's decision to require the sponsor to collect additional data in neonates and longer-term safety data in pediatric patients (b) (4)

I concur with these recommendations.

Summary –

In light of the issues discussed above, (b) (4)

I agree that, in addition to the clinical trials, it is self-evident that lipids found in Smoflipid will provide a predictable amount of energy, based on the known amount of Kcal associated with a gram of fat infused intravenously which supports the approval in adult patients. (b) (4)

I concur with this recommendation.

8. Safety

In review of the submitted trials, there was no substantive difference in adverse events between patients in the Smoflipid group and the soybean oil comparator group. It was difficult, particularly given the small trials submitted for review, to distinguish whether the adverse events observed in the trials were attributable to the lipid emulsion products administered vs the underlying condition that necessitate administration of parenteral nutrition.

Post market safety experience:

Smoflipid is approved or registered in 63 countries. The applicant reports that no actions relating to safety have been taken by regulatory authorities or the marketing authorization holder. Since first registration in 2004, the applicant estimated that 917,000 patients have been treated with SMOFlipid 20%.

The applicant submitted a Periodic Safety Update Report that covered the period from March 1, 2011 to February 28, 2014. During the reporting interval no actions have been taken or have been proposed for safety reasons. Based on the available safety data for SMOFlipid evaluated in this PSUR no change of the risk-benefit ratio of the product was identified. The clinical reviewer agreed with this finding.

Adult Clinical Trials:

The safety database for Smoflipid reflects exposure in 229 patients exposed for 5 days to 4 weeks in 5 clinical trials. The pooled population exposed to Smoflipid included adult patients up to 89 years old (20 to 89 years of age), 43% female, and 99% Caucasian. The most frequently reported medical histories in the Smoflipid group were surgical and medical procedures (84%), neoplasms (57%), gastrointestinal disorders (53%), vascular disorders (37%), and infections and infestations (20%). In the review of the submitted clinical trials, there was no substantive difference in adverse events between the Smoflipid treated patients and the soybean oil comparator treated patients. The most commonly reported adverse events were nausea 9%, vomiting 7% and hyperglycemia 5%. Sepsis was reported in both treatment groups at a rate of 2%.

Most common adverse drug reactions (>1%) from clinical trials were nausea (9%), vomiting (7%), hyperglycemia (5%), flatulence (4%), pyrexia (4%), abdominal pain (4%), increased blood triglycerides (3%), and hypertension (3%), sepsis (2%), dyspepsia (2%), urinary tract infection (2%), anemia (2%) and device related infection (2%). The rates were similar to the comparator group.

Deaths:

A total of 15 patients died in the adult studies (7 patients [3.1%] in the SMOFlipid 20% group and 8 patients [3.5%] in the comparator group). Two patients died during the treatment period and the remaining 13 patients died during follow-up. None of the SAEs leading to death in 11 of the 15 cases were considered related to the study treatment. No SAEs leading to death were

reported for the remaining 4 patients. Based on the review of patient narratives the clinical reviewer concluded that “the adult deaths occurred in patients who had undergone significant gastrointestinal surgery, and were unlikely related to the study drug.”

Pediatric Clinical Trials

In Study 00-SMOF-002, one patient in the Intralipid group experienced a severe adverse event (AE) of pyrexia; otherwise all other all AEs were of mild or moderate intensity. One serious AE (SAE) occurred in the Smoflipid group (femur fracture) and one SAE in the Intralipid group (Campylobacter gastroenteritis). All AEs were considered as unlikely related to the study medication and the patients completely recovered. There were no SAEs leading to death in study 00-SMOF-002 in children.

In Study 00-SMOF-004, the number of adverse events were similar between treatment groups with the most common adverse events being infections, infestations, and respiratory, thoracic and mediastinal disorders such as apnea. All AEs were of mild to moderate severity. Evaluation of the laboratory safety parameters did not reveal noticeable differences between the treatment groups. There were no SAEs leading to death in study 00-SMOF-004 preterm neonates.

The Study 00-SMOF-005, the most common AEs were infections and infestations (5 patients in the Smoflipid group and 11 patients in the Intralipid group), metabolism and nutrition disorders (5 patients vs. 8 patients), hepatobiliary disorders (4 patients vs. 7 patients), and blood and lymphatic system disorders (6 patients vs. 4 patients). Although there were a higher percentage of AEs in the Intralipid group compared to the Smoflipid group, the study numbers were too small to demonstrate a difference between the treatment groups. The most frequent AEs by System Organ Classes were metabolism and nutrition disorders (5 Smoflipid vs. 8 Intralipid), infections and infestations (5 vs. 11), blood and lymphatic system disorders (6 vs. 4) and hepatobiliary disorders (4 vs. 7). The most frequent events in preferred terms were hyperbilirubinemia and metabolic acidosis.

Four patients (2 patients in the SMOFlipid 20% group and 2 patients in the Intralipid 20% group) died in the preterm neonate studies (all deaths occurred in the 03-SMOF-005 study). All 4 patients who died were male. The 2 SMOFlipid 20% patients were lighter in weight (0.6 kg and 0.6 kg) than the 2 Intralipid 20% patients (1.0 kg and 1.1 kg). In the SMOFlipid 20% group, the deaths occurred during treatment, while in the Intralipid 20% group, the deaths occurred during follow-up. One SAE in an Intralipid 20% preterm infant who died was considered related to the study treatment (Enterobacter sepsis). Based on the review of patient narratives the clinical reviewer concluded that “the pediatric deaths appeared to be the result of events related to prematurity, and were unlikely related to the study drug.”

As described above additional chemical/analytical studies and clinical trials are necessary post-marketing in order to further assess the safety of Smoflipid as it is related to the effect of phytosterols and the potential risk of PNALD and PNAC. The post-market required (PMRs) studies are listed below.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of liver injury in pediatric patients including neonates, which may be related to the presence of phytosterols, with the use of Smoflipid (lipid injectable emulsion).

3002-3 Test the three registration stability batches for the individual component phytosterol content in Smoflipid (lipid injectable emulsion) using the validated analytical methods.

3002-4 Test for the individual component phytosterol content in all batches of Smoflipid (lipid injectable emulsion) manufactured over a three year period, using the validated analytical method. Based on these test results, establish safety limits for each of the individual component phytosterols in Smoflipid (lipid injectable emulsion) product specification.

3002-5 Develop and validate an appropriate analytical method for measuring phytosterol levels in plasma.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to [REDACTED] (b) (4) of a serious risk of liver injury including either parenteral nutrition-associated liver disease (PNALD) or intestinal failure-associated liver disease (IFALD) in pediatric and neonatal patients, which may be related to the presence of phytosterols. In addition, only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of sepsis and mortality. The following required clinical trials are to address these issues.

3002-6 Randomized clinical trial in hospitalized adult patients receiving either Smoflipid 20% (lipid injectable emulsion, USP) or other standard-of-care IV lipid emulsions to evaluate clinical safety outcomes of sepsis and mortality. The trial will also evaluate the requirement for ventilator support and length of stay in ICU and hospital.

3002-7 Randomized controlled trial in pediatric patients, including neonates, comparing a phytosterol-depleted formulation of Smoflipid (lipid injectable emulsion) and another standard-of-care lipid emulsion ([REDACTED] (b) (4) soybean oil product) to evaluate the incidence of liver injury, including either parenteral nutrition-associated liver disease (PNALD) or intestinal failure-associated liver disease (IFALD). An adequate number of patients should receive treatment with parenteral nutrition for at least 90 days. This trial should be initiated after the results from PMRs 3002-1, 3002-2, and 3002-3 are available. The phytosterol content of the phytosterol-depleted formulation of Smoflipid (lipid injectable emulsion) should be documented using validated analytical assay methods developed under PMR 3002-3. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 3002-5.

3002-8 Randomized clinical trial comparing SMOFLIPID (lipid injectable emulsion) to another standard-of-care IV lipid emulsion, evaluating long-term risk of developing essential fatty acid deficiency (EFAD) and parenteral nutrition associated liver disease (PNALD) in

adult patients receiving chronically-administered total parenteral nutrition (TPN). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 3002-5.

9. Advisory Committee Meeting

This product was not considered to be an NME upon submission and was not referred to the Advisory Committee.

10. Pediatrics

Review of the pediatric data is described in efficacy and safety sections above. The DPMH reviewer summarized the regulatory issues as follows:

Agreed iPSP:

“The initial iPSP was submitted on November 27, 2013 and reviewed by the PeRC on February 12, 2014. DGIEP had not reached agreement on the iPSP prior to NDA submission; however because of overall shortage issues with lipid emulsions and since the sponsor had been very responsive in attempting to resolve the issues with the iPSP, DGIEP agreed that the lack of an agreed iPSP would not constitute a refuse to file (RTF) issue. The agreed initial Pediatric Study Plan (iPSP) was submitted on November 24, 2014. The Pediatric Review Committee (PeRC) reviewed the agreed iPSP on December 17, 2014 and concurred that the agreed iPSP was adequate.”

“The iPSP includes two studies, a safety and efficacy study of Smoflipid 20% compared to Intralipid 20% in hospitalized neonates requiring parenteral nutrition for 28 days and a 3-month open-label study in infants, children and adolescents who require parenteral nutrition to collect long-term safety information. The primary objective of the study in neonates will be to collect safety data, with efficacy as a secondary endpoint. The sponsor has conducted 3 pediatric studies, which are submitted with this application. (b) (4)

[Redacted]

[Redacted] (b) (4)

(b) (4)

PeRC met on October 14, 2015 and agreed on the plan for the deferred pediatric studies outlined below.

PREA:

It was determined that Smoflipid triggers the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). Based upon the above review of the pediatric data it was determined that the following studies should be required under PREA.

DGIEP is deferring submission of your pediatric studies until 2019, because this product is ready for approval for use in adults and the pediatric studies have not been completed. As mentioned above, we have determined that the clinical data submitted in this application is insufficient and a determination of safety and efficacy is not established. Therefore, the following PREA studies are required.

3002-1 A prospective, randomized, controlled, double-blind, parallel-group study to compare the safety and efficacy of Smoflipid (lipid injectable emulsion) to standard-of-care soybean oil based lipid emulsion in hospitalized neonates including low birth weight and very low birth weight neonates. The study must enroll an adequate number of patients who receive parenteral nutrition (PN) for at least 28 days. Continue treatment for all patients who remain on PN for up to 84 days and follow-up 8 days after receiving the last dose of study treatment. The efficacy evaluation should include anthropomorphic measures and the risk of developing essential fatty acid deficiency (EFAD). Full essential fatty acid profiles should be evaluated according to standards set by major national reference laboratories. Genetic polymorphisms in the fatty acid desaturase genes (FADS) FADS1 and FADS2 should be determined in at least a subset of patients. The cut-off values for EFAD (e.g., suspected, mild and severe) should be established prior to the study. Secondary endpoints should include incidence of major neonatal morbidities, including BPD (bronchopulmonary dysplasia), ROP (retinopathy of prematurity), IVH (intraventricular hemorrhage), PVL (periventricular leukomalacia), NEC (necrotizing enterocolitis), and late-onset sepsis in premature and low birth weight neonates. The study's safety assessments should include evaluation of the risk of developing parenteral nutritional associated liver disease (PNALD) and parenteral nutrition associated cholestasis (PNAC). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 3002-5.

3002-2 Randomized controlled trial to evaluate the safety and efficacy of Smoflipid (lipid injectable emulsion) administered for at least 90 days in pediatric patients, compared to standard of care soybean oil based lipid emulsion administered for the same duration. Continue treatment for all patients who remain on parenteral nutrition (PN) for up to 1 year. The study should enroll an adequate number of patients 3 month of age and older. The study's efficacy assessments should include anthropomorphic measures and evaluation of the risk of developing essential fatty acid deficiency (EFAD). Full essential fatty acid profiles should be

evaluated according to standards set by major national reference laboratories. Genetic polymorphisms in the fatty acid desaturase genes (FADS) FADS1 and FADS2 should be determined in at least a subset of patients. The cut-off values for EFAD (e.g., suspected, mild and severe) should be established prior to the study. The study's safety assessments should include evaluation of the risk of developing parenteral nutritional associated liver disease (PNALD) and parenteral nutrition associated cholestasis (PNAC). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 3002-5.

These studies should provide data which is of sufficient duration to assess the potential risk of essential fatty acid deficiency disease (EFAD), and the risk of developing parenteral nutritional associated liver disease or cholestasis (PNAC or PNDALD), as well as monitor for additional safety adverse reactions.

11. Other Relevant Regulatory Issues

- Fixed combination drug-product

Smoflipid (lipid injectable emulsion) is a combination of (b) (4) lipids, specifically: soybean oil (6%), olive oil (5%), medium chain triglycerides (6%) and fish oil (3%). The applicant intentionally combined these oils, each at a specific concentration, (b) (4)

(b) (4) We have determined that this is a fixed- combination drug product subject to application of the Agency's regulations on fixed- combination drugs.¹⁷

The professional labeling states that Smoflipid is indicated "in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated." No clinical outcome claims are included in this indication. The ability of the product to provide the purported nutritional support is self-evident by assessing the product's component oils. The product is intravenously infused, and the amounts of calories provided can be determined based on the amount of lipids contained in the product, since it is a well-established scientific fact that the energy content of lipids is 9 kcal/g. For adults, there is sufficient delivery of essential fatty acids, Linoleic Acid (LA) and alpha-Linolenic acid (ALA), in this product to achieve daily oral intake recommendations. Guidelines vary, however; for example, assuming LA intake ranges from (b) (4)% of total energy intake and ALA ranges from (b) (4)% of total energy intake, Smoflipid would provide an excess of LA and ALA based on the total fat calories required daily in adults. The sponsor submitted 5 randomized, active control clinical trials of Smoflipid in adults, three of which compared it to a formulation with only soybean oil in adults. As noted in the section on "Adult Clinical Studies" in this review, these studies were not adequately designed and powered to establish the nutritional equivalence or superiority of Smoflipid to Intralipid, and no study established that Smoflipid is superior or non-inferior to the Intralipid control on a

¹⁷ See 21 CFR 300.50. Under FDA's regulations on prescription fixed-combination drugs, "[t]wo or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."

clinical outcome measure. As discussed in the Clinical Review, the sponsor was seeking approval of Smoflipid only for the “provision of energy support,” and thus seeking an indication “in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated,” an indication that included no clinical outcome claims. The clinical review team thus focused the review of safety and efficacy only on whether the studies provided evidence to support a claim as a source of calories and essential fatty acids. As noted in both the clinical review and in this review, Smoflipid’s ability to provide the claimed nutritional support is self-evident by assessing the product’s component contents, i.e., the amount of calories provided can be mathematically determined based on the amount of lipids present in the product. In that regard, these studies provide clinical information regarding laboratory and clinical assessments that demonstrate that the lipids administered are being metabolized, and there were no unexpected serious safety issues seen. No cases of essential fatty acid deficiency (EFAD) were found in the adults enrolled in the studies. These studies provided sufficient information indicating that the Smoflipid lipid emulsion was bioavailable and provided energy support. Specifically, we relied on the following studies performed by the applicant to determine the safety and efficacy of Smoflipid for the indication: FE-SM-03-DE, FE-SM-04-CH, 03-3CB7-001, 03-3CB8-001, and 05-SMOF-006. Other than the indication, no other claims of superiority or non-inferiority were added to the label. (b) (4)

We have determined that the applicant would not be required to perform a full factorial design trial¹⁸ based on the fact that with respect to the proposed indication (provision of energy calories and essential fatty acids), the contribution of each component to the claimed effects of the fixed-combination is that they provide energy, and in the case of soybean oil and olive oil, energy and EFAs. In other words, the total energy supplied in Smoflipid is derived from the calories supplied from each oil included in the injectable emulsion. There were no unexpected serious safety concerns with combined use of the component oils. There are theoretical concerns (b) (4)

None of these considerations are currently claimed by the applicant, nor are they found in the product labeling. In discussions with Fresenius-Kabi, DGIEP requested them to describe what studies could be used to fulfill the fixed-dose drug combination rule. The sponsor submitted a response on October 27, 2015, that included published literature. However, considering the indication, DGIEP did not rely on the published literature or other information submitted in the sponsor’s October 27 response, but relied only upon the studies listed above, conducted by the sponsor, in determining efficacy and safety in adults.¹⁹

- Financial Disclosure, all were found to be appropriate and complete.
- Other consults-
 - **CDRH/OCE/DAGID, General Hospital Device Branch consult:**

¹⁸ Id. Specifically, under 21 CFR 300.50 each component in a fixed-combination must make a contribution to the claimed effects of the fixed-combination.

¹⁹ I further note that to the extent any of the reviews referenced literature, the references were for background purposes only. It was not necessary to rely on literature to support approval of the application.

An engineering review of the (b) (4) bag to be used with the Smoflipid product was performed regarding the container closure device/system. This reviewer found the bag to be acceptable for this application.

- **Office of Scientific Investigations:** Site inspections related to five studies were conducted (Protocol 00-SMOF-004, Protocol FE-SM-04-CH, Protocol 03-SMOF-005, Protocol FE-SM-03-DE, Protocol 00-SMOF-002) were found satisfactory
- **OPDP:** provided labeling comments which were considered during labeling negotiations.
- **DMEPA:** Proprietary name Smoflipid acceptable. “We note that you submitted your proposed proprietary name with the letters “SMOF” capitalized and the remainder of the name in lowercase letters. This mixed case presentation (tall man lettering) is typically reserved for differentiating look-alike names that have been confused in the marketplace. Since Smoflipid is not a name that has been involved in drug name confusion or wrong drug errors, the letters “SMOF” in your proposed proprietary name should not be capitalized in your labels and labeling.” The applicant agreed to the change.

There are no unresolved relevant regulatory issues

12. Labeling

- Proprietary name: Smoflipid was found acceptable.
- Established name, lipid injectable emulsion (consistent with current USP monograph) was found acceptable.
- Physician labeling
 - **DPMH** (maternal health team) “recommends labeling language for 8.1 which conveys the paucity of clinical trial data on the benefit–risk of TPN administration during pregnancy; however, the labeling should also include a Clinical Considerations section that describes the use of TPN with a lipid infusion in instances where pregnant women are unable to consume adequate nutrients to maintain their weight.” Further regarding lactation in labeling they have the following recommendations: There are no data on the safe use of TPN during lactation nor are there reports of serious adverse events. Therefore, the benefits of breastfeeding should be considered in a lactating woman receiving TPN. DPMH recommends labeling language which conveys to healthcare providers the need for a benefit/risk assessment of Smoflipid use during lactation”. The team participated in the labeling discussions.
 - **DMFH** (pediatric team)
The pediatric consult recommended that “(b) (4) information on pediatric studies should be restricted to section 8.4 Pediatric Use with the exception of specific risks that have been

identified in pediatric patients (see Boxed Warning and Warnings and Precautions in the approved professional labeling). A summary of information these specific safety concerns should be included in 8.4 with the appropriate cross-reference to Warnings and Precautions. The risk of death from exposure to lipid emulsions in neonates is a class effect and is included as a boxed warning in Intralipid, Nutrilipid and Clinolipid lipid emulsions and Kabiven/Perikabiven a combination product with amino acids, electrolytes, dextrose and lipid injectable emulsion, and is appropriate here. The indication notes that the product is only approved for use in adults. Limitations of use, if appropriate, are generally included under section 1. DPM does not recommend a limitation of use for this product because we do not want to discourage use in a shortage situation or if a provider elects to use the product in a patient with PNALD (as discussed above). The warnings above, with the exception of information on monitoring for EFAD, are common to the approved lipid emulsions, Intralipid, Nutrilipid and Clinolipid and to Kabiven/Perikabiven (amino acids, electrolytes, dextrose and lipid emulsion combination). Clinolipid and Kabiven/Perikabiven, unlike Intralipid and Nutrilipid, are not approved in pediatrics; both include an additional warning that laboratory monitoring is needed for EFAD. This warning is also appropriate for Smoflipid since there was insufficient data in pediatric studies to confirm that EFAD does not occur with the use of Smoflipid. (b) (4)

[REDACTED] a statement is included in section 8.4 that safety and effectiveness have not been established in the pediatric population and any information on the studies is limited to this section. Cross-reference to the appropriate W&P that apply to pediatric patients are included in 8.4. ”

I agree with these recommendations, including not listing limitations of use for pediatrics in this label. The data that was presented in this application, although inadequate to approve the pediatric indication, did not show significant differences or imbalances in Holman index or other safety events.

Limitations of use section includes information that the fatty acid ratio was considered necessary to assure that the health care provider understands that substantial evidence does not exist to support that the olive oil, medium chain triglycerides or fish oil impart special qualities that would result in improved clinical outcomes related to anti-inflammatory effects or favorable immune modulatory effects or claims.

In order to reflect this fact the Limitations of Use section includes this statement:

“The omega-6: omega-3 fatty acid ratio and Medium Chain Triglycerides in Smoflipid have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions”.

It also refers the reader to the Clinical Studies Section (14) which contains the following wording:

“Although Study 1, Study 2, and Study 3 were not adequately designed to demonstrate non-inferiority of Smoflipid to the soybean oil comparator, they support Smoflipid as a source of calories and essential fatty acids in adults”.

- Carton and immediate container labels: it is permissible to have the following appear on the carton and container: Smoflipid (lipid injectable emulsion) 20%
- Professional Label: according to internal guidance, the name that appears in the professional label will be SMOFLIPID (lipid injectable emulsion), for intravenous use.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

- Approval of the proposed indication for adults. The sponsor has demonstrated Smoflipid to be safe and effective in adult patients for the approved indication. (b) (4)

Risk Benefit Assessment

I concur with the reviewers that Smoflipid provides intrinsic nutritional value that outweighs the potential risks, and recommend approval of this NDA. Substantial evidence that the new lipid emulsion comprised of (b) (4) olive oil, (b) (4) soybean oil, medium chain triglycerides and (b) (4) fish oil, Smoflipid, provides a clinically meaningful advantage over the currently marketed (b) (4) soybean oil product was not provided in this NDA. The applicant also did not conduct non-inferiority trials designed and powered to establish that Smoflipid is statistically non-inferior to the available approved therapy on a specific clinical benefit endpoint. However, humans require energy to sustain life and also require essential fatty acids. The clinical trials, together with generally accepted scientific knowledge, support a finding of substantial evidence of effectiveness for the proposed indication. Smoflipid is a fat emulsion that provides an objectively documented level of kcal (energy) and contains essential fatty acids. It is self-evident that Smoflipid is a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. The risk of developing essential fatty acid deficiency with Smoflipid, (b) (4) is greatest in children. (b) (4)

Clinical trials will be required under Food and Drugs Agency Amendment Act (FDAAA) to evaluate the risk of EFAD. Smoflipid and other lipid emulsion products contain phytosterols as an impurity. Phytosterols have been linked to liver injury. Studies and clinical trials will be required under FDAAA to address this safety issue. A clinical trial will also be required to assess the risk of sepsis and mortality with the use of Smoflipid. (for complete list of PMRs see approval letter)

- **Postmarketing Risk Evaluation and Mitigation Strategies (REMs):** Based upon the risk-benefit profile described above, it was determined that there was no need for a REMS.

- **Recommendation for Postmarketing Requirements** (as listed above, also see approval letter)

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/s/

JOYCE A KORVICK
07/13/2016