CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204508Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA #	204508
Applicant Name	Baxter Healthcare Corporation
Date of Submission	January 3, 2013
PDUFA Goal Date	October 3, 2013 (includes 3-month extension based on major amendment received 6/07/2013)
Proprietary Name / Established (USAN) Name	Clinolipid 20% Lipid injectable emulsion, USP
Dosage Forms / Strength	20% Lipid injectable emulsion
Proposed Indication(s)	For parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Klaus Gottlieb, MD
Pharmacology Toxicology Review	Dinesh Gautam, PhD/Sushanta Chakder, PhD
CMC Review	Tarun Mehta
Product Quality Microbiology Review	Denise A. Miller/Bryan Riley, PhD
Clinical Pharmacology Review	Kristina Estes, PharmD/Sue Chih Lee, PhD
OPDP	Meeta Patel, PharmD
CDTL Review	Robert Fiorentino, MD
OSE/DMEPA	Denise Baugh, PharmD, BCPS/Lisa Khosla, PharmD, MHA/Lubna Merchant, MS, PharmD/Carol Holquist, RPh
PMHS	Alyson Karesh, MD/Leyla Sahin/Hari Cheryl Sachs, MD/Jeanine Best/Lynne Yao, MD
CDRH/Office of Device Evaluation/General Hospital Devices Branch Human Factors	Jason To Quynh Nguyen

OND=Office of New Drugs
CDRH=Center for Devices and Radiological Health
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
PMHS=Pediatric and Maternal Health Staff
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion

Division Director Review

1. Introduction

This 505(b)2 NDA proposes a new lipid injectable emulsion product. The drug substances used in the product are refined soybean oil and refined olive oil, in a 1:4 ratio of soy oil to olive oil. The product referenced in this NDA is Intralipid 20%, which is a lipid injectable emulsion product that contains only soybean oil. It was approved in 1981. As presented in the CMC review, the USP definition of lipid injectable emulsion is, "The most frequently used oil 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 oils(s). It contains no antimicrobial agents. The final products are terminally sterilized". The following table summarizes the fatty acid composition of olive oil and soy oil in Clinolipid (lipid injectable emulsion, USP) 20%.

Table 1. Fatty acid composition of each component oil in Clinolipid 20%

Fatty acid	Carbon chain length	Number of double bonds	Olive	Soy
Palmitic	16	0	7.5 – 20.0%	9 – 13%
Palmitoleic	16	1	≤ 3.5%	≤ 0.3%
Stearic	18	0	0.5 – 3.5%	2.5 – 5%
Oleic	18	1	56 - 85%	17 – 30%
Linoleic	18	2	9 - 13%	48 – 58%
Linolenic	18	3	≤ 1.2%	5 – 11%
Arachidic	20	0	≤ 0.5%	≤ 1.0%
Eicosenoic	20	1	≤ 0.4%	≤ 1.0%
Behenic	22	0	≤ 0.2%	≤ 1.0%
lignoceric	24	0	≤ 0.2%	≤ 0.5%
erucic	22	1	---	≤ 0.3%
myristic	14	0	---	≤ 0.2%

Clinolipid (lipid injectable emulsion, USP) 20% provides a lower percentage of the essential fatty acids linoleic acid and linolenic acid, compared to the referenced product.

The application was designated a priority review due to an ongoing shortage of lipid emulsion products. The review clock was extended 3 months, based on a major amendment received on June 7, 2013.

2. Background

Intravenous lipid emulsions are intended for 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. Administration of lipid emulsions to these patients reduces the amount of glucose that would otherwise have to be administered to achieve the necessary calories per 24 hour period. Administration of high dextrose loads contributes to hyperglycemia in critically ill patients, and has been associated with higher risk for morbidity/mortality. (Olveira G, et al. Diabetes Care. May 2013, Vol 36 no. 5: 1061-1066) Lipid emulsions are also intended to supply patients with essential fatty acids (EFA).

Intralipid, the reference product, received marketing approval as a 10% solution in 1975 and as a 20% solution in 1981. The 10% product is rarely used because the higher concentration of free phospholipid in the 10% formulation relative to the 20% product interferes with lipoprotein lipase activity (Mirtallo, et al. Annals of Pharmacotherapy. 2010 April, Volume 44: 688-700), and has been associated with a higher rate of adverse events.

The 1975 Division Director review recommending approval of Intralipid 10% indicates that the decision to approve was based on the fact that the product provided a known amount of calories, based on the amount of fat present, and because it was a source of essential fatty acids. Dr. Margaret Clark's review ends with:

> "Intralipid not only provides 9 calories per gram but has intrinsic nutritional value in the fatty acids, especially linoleic acid. It may be administered via a peripheral vein and is isotonic. The availability of this product will permit the physician to provide a complete diet by a route extrinsic to the gastrointestinal tract.
>
> Satisfactory information with regard to manufacturing controls, preclinical data, and clinical studies has been submitted. The labeling, with the revision noted in the proposed letter to the firm, will provide for the safe and effective use of this drug."

Dr. Clark's summary review of the clinical studies submitted to support the application indicates similarity to the types of studies submitted in support of the current NDA for Clinolipid, with similar limitations in terms of design and power. There were 67 studies submitted in support of the Intralipid 10% NDA, described by Dr. Clark as follows:

> "Four of the studies were performed on 22 normal adult volunteers and the remaining 63 on 298 patients, 128 adults and 170 children, mostly infants suffering from GI diseases impairing food absorption, from burns or from essential fatty acid deficiency secondary to chronic use of parenteral nutrition without fats. Forty-two of the studies were performed on an emergency protocol and had only 1-3 patients (30 studies). Seven of the studies were controlled and used 46 adults and three children. The remaining 56 studies were uncontrolled and used 62 adults and 148 children."

The sample size in each of the controlled trials was small. Her review indicates most of the trials were less than 10 patients in size. One trial enrolled 15 patients, and another enrolled 12.

(b) (4) "ClinOleic 20% Injectable emulsion, " which is marketed outside the US and has been available since 1995.

3. CMC

Manufacturing site inspections resulted in a finding that the sites were "acceptable". The product quality microbiology reviewer recommended approval. Although the CMC reviewer ultimately recommended approval, the CMC review team initially did not recommend approval because: 1) the drug product specification needed to be revised according to Draft ICH Q3D guidance for elemental impurities in large volume parenterals, and 2) the CDRH consult review had not deemed the container closure system adequate. Although the product proposed for marketing in this NDA conformed to the USP monograph for Lipid Injectable Emulsion, the reviewers voiced concern over potential exposure to high levels of elemental impurities. For this reason, the applicant was asked to revise the drug product specification to conform to the new draft ICH Q3D requirements for elemental impurities.

All excipients, with the exception of sodium oleate, are subject to NF/USP compendial monographs. The applicant classified sodium oleate as a novel excipient because it has never been intentionally added to a US pharmaceutical drug product. The Pharmacology/Toxicology review team reviewed it as a new excipient and found no safety concerns.

While the above initial review concerns of the CMC reviewer were ultimately adequately addressed, additional concerns about the drug product and the container/closure system arose during the review period. These issues are summarized below.

Phytosterol content in the drug product. Clinolipid (lipid injectable emulsion, USP) 20% contains phytosterols (as does the reference product), and phytosterols have been linked to the development of parenteral nutrition associated liver disease (PNALD). The CMC reviewers noted that phytosterols are a product impurity, and contacted the applicant to request addition of testing and limits for phytosterol content to the drug product specification. Because phytosterols have been linked to the development of PNALD (a serious risk of liver injury), testing the product with a validated assay and setting limits for the presence of individual component phytosterols were deemed safety issues, necessitating that these product quality issues be addressed as studies required under 505(o). In addition, a clinical trial to identify a serious risk of liver injury in pediatric (including neonatal) patients will be required as a PMR under FDAAA. As it is currently unknown whether a specific phytosterol(s) is entirely responsible for the risk and because the safe threshold level is unknown, the Clinical team recommended that the applicant be required to incorporate a Clinolipid product depleted of phytosterols in this clinical trial. See the end of this Section and Sections 8 Safety for details on these PMRs.

As stated earlier in this review, the currently marketed lipid emulsion products also contain phytosterols. This safety issue, as it applies to these other products in this class, will also be

addressed with letters to the NDA holders for those products. See Section 11 Other Regulatory Issues.

Container/Closure. The finished drug product is packaged in a (b) (4), (b) (4), polyolefin container closure system, CLARITY (PL 2401-1). The extractable and leachable testing and results were reviewed by the CMC reviewers and the Pharmacology/Toxicology reviewers. Safety concerns regarding extractables/leachables were adequately resolved in this review cycle. In addition, the applicant agreed to the following in an amendment to the NDA, dated May 6, 2013:

> "the applicant will establish the change control protocol through a supplement for monitoring any future changes in the container closure's manufacturing process and/or any raw material"

This is documented as an additional comment in the approval letter.

During the course of the review, on July 16, 2013, there was a Health Canada Advisory posted which reported the potential "presence of particles from the administration port material" for the NDA proposed product, which is currently marketed in Canada with the name Clinoleic 20%. The following was communicated in the Advisory:

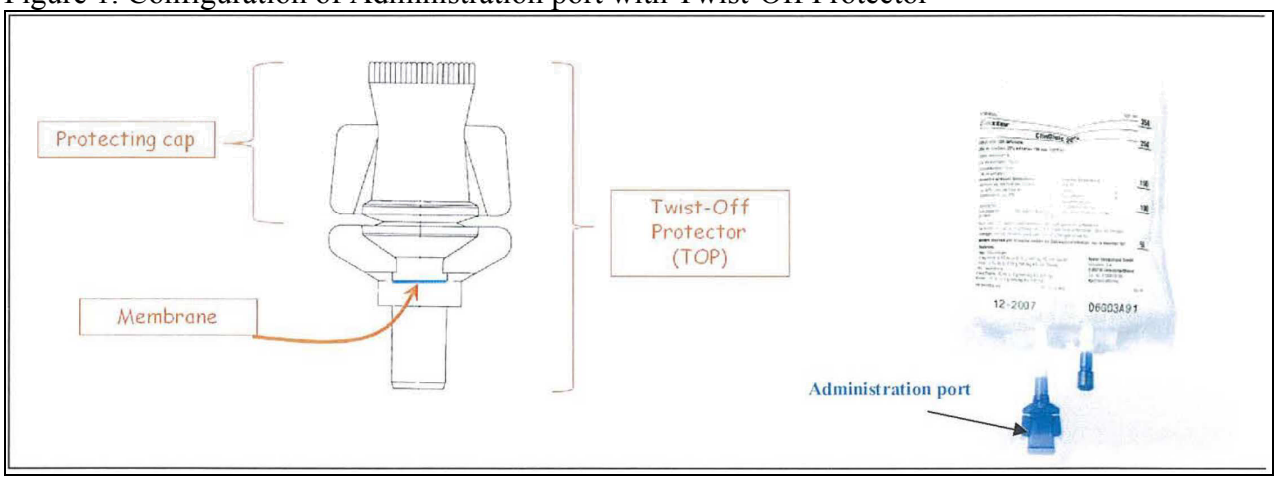
> *Baxter Corporation has recently received product complaints in Canada for full detachment of the sterile blue membrane in CLINOLEIC 20% emulsion after spiking with a transfer or administration set.*
> - *Detachment of the sterile blue membrane in CLINOLEIC 20% emulsion can occur after spiking the administration port. This could potentially result in particulate matter entering the emulsion.*
> - *Particulate matter (greater than 5 micron) has the capability of obstructing blood flow through capillaries, which could lead to complications such as embolism.*
> - *In accordance with the American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines for Parenteral Nutrition formulations, Baxter recommends that in-line filters should be used on administration sets regardless of Parenteral Nutrition formulation (i.e. Total Nutrient Admixture or separate IV Lipid Infusion) or clinical setting (i.e. by patients in home use or hospitals and clinics) in order to mitigate the risk of particulate matter during infusion.*

The Health Canada Advisory recommended that when administering Clinoleic, clinicians should follow the ASPEN Guidelines for PN Formulations, which recommend use of a 1.2 micron in-line filter for PN formulations with lipids. If the administration set to be used does not have a 1.2 micron filter, Health Canada recommended adding a 1.2 micron filter extension set to the administration set.

FDA asked the applicant to provide detailed information regarding this administration port issue. A detailed summary of the response, with supporting figures, can be found in the CDTL review. The applicant had received 4 complaints of "particulate matter" generated on spiking

of the ClinOleic product bag. The events were associated with a specific compounding set and a specific administration set. The particulate matter was "the entire membrane disc from the twist off protector closure." The applicant's medical risk assessment considered the actual risk to patients low because 1.2 in line filters are already recommended by ASPEN/ESPEN, and "are typically used to administer lipids."

Figure 1. Configuration of Administration port with Twist-Off Protector



The applicant's initial investigations led them to believe that specific physical attributes of individual spikes made them more or less likely to cause the dislodgment of the membrane. Their medical risk assessment identified a specific spike, spike #173, which "should not be used with ClinOleic since the spike has a sharp point on the outer edge and when rotated fully could dislodge the entire membrane."

The applicant conducted a study (study 64965) to "provide assurance on the acceptable interaction of various spikes in the US and North America with the Clinolipid TOP." There was a defined list of spikes included in testing for compatibility with the twist off protector closure, and a list of system requirements that would be verified in the study. These requirements were specific for each of the two product types associated with the spike, i.e., 1) Gravity and automated compounding products, and 2) Direct administration and dispensing products. The applicant was only able to submit a high level engineering summary of this study to FDA prior to the close of the review clock. CDRH reviewers evaluated these preliminary results, noted the applicant's response to four follow-up questions from CDRH, and acknowledged the applicant's assertion that further assessment of this study will take place in the form of an Interface Evaluation and Recommendation Report. Therefore, CDRH drew no final conclusions from the information provided in the preliminary report.

The CDRH Human Factors team, DMEPA reviewers and Clinical reviewers met to discuss the lack of definitive results and how best to address this remaining issue. The reviewers discussed the risk to patients associated with dislodgement of the membrane, and agreed that use of the inline filter would mitigate the risk. The Clinical reviewers pointed to information that professional guidelines state that an inline filter should be used with fat emulsion administration. The reviewers contacted ASPEN during the review to confirm that this is the current standard of care. The CDRH Human Factors and DMEPA reviewers expressed

concern that there is no documentation in the application of whether users consistently use an inline filter with fat emulsion products, including the proposed product. The reviewers agreed that labeling should be revised to draw attention to the need for an inline filter when this product is administered and that the pore size should be 1.2 microns, which is small enough to filter out fragments large enough to obstruct capillaries (5 microns) and large enough for the fat to traverse. In addition, all agreed that the reasons for selection of this pore size, i.e., fragments dislodged from the infusion port, should be included in the product label. The CDRH Human Factors reviewer strongly recommended that a post marketing study be performed to assess label comprehension and appropriate use of the filter in end users, including pharmacists, nurses and home health nurses (who train patients for home use). In addition, they recommended that this study evaluate the spiking procedure. Based on their recommendation, a human factors study will be included as a PMR study required under FDAAA. (See below.)

It should be noted that lipid emulsions are to be administered with administration sets and lines that don't' contain di-2-ethylhexyl phthalate (DEHP). In addition, use of final filters is recommended with parenteral nutrition products. Filters used with lipid emulsions must have a pore size ≥1.2 microns.

Summary. Ultimately, the CMC reviewers recommended approval. I concur. An expiration dating period of 18 months was granted. As discussed above, the product labeling will address the dislodgement/fragmentation issue and the use of a 1.2 micron pore inline filter in Section 2.1 Use of an Inline Filter. This section will also include a statement "Fragments of the administration port membrane could be dislodged in the bag after spiking." In addition, under Section 2.3 Mixing Guidelines, there will be a statement to address a specific spike used with a compounding machine that has been associated with dislodgement (as discussed above), "Do not use the EXACTAMIX Inlet H938173 with an EXACTAMIX compounder to transfer Clinolipid injection. This inlet spike has been associated with dislodgement of the administration port membrane into the Clinolipid injection bag."

As stated above, in light of the link of the phytosterol impurities in lipid emulsion product to PNALD, and because of the administration port membrane dislodgement issue associated with the container, the following PMR's under FDAAA, will be included in the approval letter, which will state:

> "…..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, or identify an unexpected serious risk of administration of unfiltered product that contains fragments of the product container…… Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2085-1 Develop and validate an appropriate analytical method for determining the individual component phytosterol content in Clinolipid (lipid injectable emulsion, USP) 20%.

The timetable you submitted on October 3, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/14

2085-2 Test the three registration stability batches for the individual component phytosterol content in Clinolipid (lipid injectable emulsion, USP) 20% using the analytical methods developed in PMR 2085-1 .

The timetable you submitted on October 3, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/14

2085-3 Test for the individual component phytosterol content in all batches of Clinolipid (lipid injectable emulsion, USP) 20%, manufactured over a three year period, using the method developed under PMR 2085-1. Based on these test results, establish limits for each of the individual component phytosterols in Clinolipid (lipid injectable emulsion, USP) 20% in the product specification.

The timetable you submitted on October 3, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/16

2085-4 Develop and validate an appropriate analytical method for measuring phytosterol levels in plasma.

The timetable you submitted on October 3, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/14

2085-5 Conduct a human factors study to assess user comprehension of the label's instructions to use an inline filter with pore size of 1.2 microns during administration of Clinolipid (lipid injectable emulsion, USP) 20% or an admixture containing Clinolipid (lipid injectable emulsion, USP) 20%. In addition, the study should evaluate the ability of the user to appropriately spike the product's administration port. The study should enroll representative user populations, including pharmacists, nurses, and home health care nurses.

The timetable you submitted on October 3, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/14
Study Completion:	04/14
Final Report Submission:	06/14

In addition, the applicant has agreed to four PMCs related to testing the product and setting limits for cholesterol and squalene. (See approval letter.)

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the Pharmacology/Toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. The product label will reflect the principle signs of toxicity noted in the nonclinical studies conducted in rats and dogs, which were 3 months in duration and included comparisons to soybean based lipid emulsions, e.g. Intralipid. The major observations in these studies included:

1) Hemolytic anemia at 12 g/kg/day in rats and at 6 g/kg/day in dogs (doses that are 4.8 and 2.4 times higher, respectively, than the recommended adult dose (2.5 g/kg/day) of Clinolipid.
2) Dose-dependent decrease in urea levels in rats at 6 and 12 g/kg/day dose levels and in dogs at 3, 4.5 and 6 g/kg/day dose levels.
3) Hypercholesterolemia in dogs at 3, 4.5 and 6 g/kg/day dose levels.
4) Hepatic lipid and pigmentary overload in male and female rats at 3, 6 and 12 g/kg/day, and in male dogs at 6 g/kg/day and female dogs at 3, 4.5 and 6 g/kg/day.
5) Splenic hemosiderosis and vacuolization in rats at 3, 6 and 12 g/kg/day, and dogs at 4.5 and 6 g/kg/day.

Hepatic toxicity has been associated with lipid emulsions in humans. In these nonclinical studies, at a dose of 3 g/kg/day, lipid and pigmentary overload of the liver and vacuolization of Kupffer cells were observed in rats and dogs. At a dose of 12 g/kg/day in rats, hepatocellular vacuolation, granulomatous inflammation of the liver, hepatocellular necrosis and hemosiderosis and splenic hemosiderosis, associated with a lipid load hemosiderin cells were observed. In dogs, at a dose of 6 g/kg/day, brownish-yellow pigmentation in the Kupffer cells of liver and spleen, hyperplasia, vacuolization, and an increase in the number of lipid storage cells in the liver and macrophage vacuolization of the spleen were observed.

The Pharmacology/Toxicology reviewer noted in his review that the toxicity profiles associated with Clinolipid in these nonclinical studies were comparable to the soybean oil comparator arms. He determined that local tolerance studies, utilizing subcutaneous and intradermal injection supported a conclusion that there is no potential for tissue necrosis if the product infiltrates during infusion.

Novel Excipient. With regard to the novel excipient contained in Clinolipid, sodium oleate, the reviewers noted that it "is not mutagenic, genotoxic or carcinogenic and is not a reproductive or development toxicant."

Impurities/Degradants. The following table, reproduced from the Pharmacology/Toxicology review, lists the residual solvents that are impurities present in the drug substances. The reviewers noted that according to ICH Q3C (R5), (b) (4) and (b) (4) are (b) (4) solvents and (b) (4) is a (b) (4) solvent. The permitted daily exposure (PDE) for (b) (4) solvents is (b) (4) mg ((b) (4) ppm) per day. The limit for the amount of (b) (4) plus (b) (4) present, according to the table below, falls under (b) (4) ppm. The (b) (4) PDE is (b) (4) ppm. As shown in the table, the (b) (4) limit is far less than its PDE.

(b) (4)

(b) (4)

The reviewers asked the applicant to determine the heavy (b) (4) levels in the finished drug product, which is summarized in the table below (reproduced from the Pharmacology/Toxicology review). The reviewers calculated the predicted human daily exposure (HDE in the table below, micrograms/day) for each of the elemental impurities, using a maximum daily dose of 625 ml (based on a 50 kg body weight). The calculated HDEs, based on the assay quantitation limit (since nothing was detected), were lower than the PDEs. Although a relatively low body weight for US population, 50 kg, was used for these calculations, there is a several fold difference between the HDE and PDE for each elemental impurity. The smallest fold difference was for (b) (4) and even it had a reasonable "margin": HDE (b) (4) microgram/day vs. PDE (b) (4) microgram/day.

Table 3.

Summary of Elemental Impurities Risk Assessment

Code Number	Elemental Impurity	Experimental Value (ng/mL)[1]	Quantitation Limit (QL, ng/mL)[1]	HDE (µg/day)[2]	PDE (µg/day)	Is the HDE < PDE?
(b) (4)	(b) (4)					(b) (4)

QL = Quantitation limit for the standards prepared on the day of analysis.
HDE = Human Daily Exposure
PDE = Permissible Daily Exposure. Reference 2.
[1] Testing was performed on three units from each of the 3 respective primary stability batches manufactured in support of NDA 204508. Reference 8. No values were observed above the QL.
[2] Calculated as [(QL (ng/mL) x 625 mL/day) / (1000 ng/µg)]

The nonclinical reviewer noted that although the (b) (4) impurities PDEs were obtained from the draft ICH Q3D guidance, (b) (4) aren't listed in the guidance. For those limits, the reviewers looked to the current EMEA guidance for the PDEs. The HDE levels were also found to be within acceptable limits for these (b) (4).

I agree with the CDTL review statement regarding the Pharmacology/Toxicology review summary statements on the applicant's submitted *in vitro* study on immune function in peripheral white blood cells and an *in vivo* study of lymphocyte activation in rats, in which the CDTL stated, "I consider these statements to be speculative in nature as the applicant has provided evidence that Clinolipid offers no advantages with respect to being less 'pro-inflammatory' than other IV lipid emulsions."

5. Clinical Pharmacology

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

The Clinical Pharmacology reviewers reviewed the proposed labeling and recommended revisions, which were incorporated. I concurred with their recommendations. The reviewer reviewed the results of 4 clinical pharmacology studies that were considered exploratory. The data from the studies, which were not necessary for NDA approval, were considered of limited

value and the reviewer recommended that these data should not be included in labeling. I concur.

The applicant proposed content for Section 7 Drug interactions of the product label, stating that olive and soybean oils contain "Vitamin K1 that may counteract the anticoagulant activity of coumarin derivatives, including warfarin." The reviewers concurred with including this statement in Section 7.

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

Although the applicant provided the results of 31 studies and clinical trials, there were only 9 controlled studies (in which Clinolipid was compared to the currently marketed lipid emulsion product, Intralipid) in adult patients, and only 3/9 were of duration longer than 5 days. One of those 3 only treated 3 patients. The Clinical reviewers focused on the remaining two studies for the efficacy review (in which only a total of 48 patients were treated in one and 22 in the other). No formal statistical review was conducted. The statistical reviewer stated in his filing review,

> "No individual clinical study submitted appears to be identifiable as pivotal for efficacy review and labeling purposes. 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 objectives and design of the two major randomized, controlled trials reviewed are summarized in the table below, which is reproduced and modified from the CDTL review. Both were open label. Prolonged or long term use was defined as ≥15 days in one (which had as objectives: assessment of both efficacy and safety) and ≥ 26 days in the other (which had as its objective: assessment of safety). The efficacy trial included hospital patients, while the safety trial included both hospital and ambulatory patients. Although the second trial's major objective was assessment of safety, both trials collected data on weight, arm circumference and skin fold thickness which were relevant to the efficacy review of this NDA.

Table 4. Completed Controlled Studies Comparing Clinolipid to Intralipid in Adult Patients

Study ID	Objective	Design	Treatments	Number Of Subjects	Patient population	Duration
C 89 CSW 6/3 08 F*	Evaluate efficacy and safety with prolonged use (≥ 15 days)	Multicenter, randomized, open label, active control	ClinOleic versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day)	48 planned 48 treated 24 ClinOleic, 24 Intralipid	Hospital patients requiring total parenteral nutrition	15 days to 6 months
C 89 CSW 6/3 10 F*	Evaluate safety with long-term use (≥ 26 days)	Multicenter, randomized, open label, active control	ClinOleic versus Intralipid adjusted to caloric need	50 planned 22 treated 12 ClinOleic, 10 Intralipid	Hospital or ambulatory patients requiring supplemental parenteral nutrition	26 days to 1 year

In the larger, efficacy and safety trial, the two treatment groups had similar results in anthropometric criteria, including body weight, arm circumference and skin fold thickness. In addition, mean total serum protein and albumin increased similarly in the two groups.

In the smaller safety trial, the mean duration of treatment with Clinolipid was 202 days (range 24-408) and 145 days in the comparator group (range 29-394 days). The two treatment groups had similar outcomes in weight, weight loss, mid-arm circumference and skinfold thickness (triceps).

The Clinical reviewer also examined the various metrics of nutrition (including albumin, prealbumin, nitrogen balance, anthropometrics, essential fatty acids, triglycerides, fatty acids) across the various trials submitted for review, in addition to biomarker measures of inflammation and oxidation. The latter assessments were evaluated by the applicant in an effort to demonstrate a potential advantage of Clinolipid over other lipid emulsions based on impact on inflammation and immune function. Although there were 23 completed studies in which 386 adult and 198 pediatric patients were treated with Clinolipid, the individual studies were small, and pooling the data was not considered appropriate. Therefore, no valid conclusions could be drawn.

In summary, none of the submitted trials were adequately designed and powered to establish nutritional equivalence or superiority of Clinolipid to the currently marketed lipid emulsion products. No study established that Clinolipid is superior or noninferior to available therapy on a clinical outcome measure. However, the applicant's full proposed indication was: "indicated for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. As a lipid emulsion, ClinOleic 20% provides a source of calories and essential fatty acids for patients requiring parenteral nutrition." No clinical outcome claims were included in this proposed indication. The Clinical reviewer concluded that the

failure to establish superior or noninferior efficacy in the trials submitted to support this NDA is not an approval issue, because the product's ability to provide the purported nutritional support 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 that the energy content of lipids is 9 kcal/g. I concur, with regard to the provision of calories. The product does contain essential fatty acids (EFA); however, there are concerns about the adequacy of the amount of essential fatty acids it provides, particularly for children. This is discussed further in this section of my review, as well as in Section 8 Safety.

With regard to dose, the applicant based the labeled dose on ASPEN guidelines [Task Force for the Revision of Safe Practices for Parenteral Nutrition. JPEN; J Parenteral Enteral Nutr 2004, 28:S39. PMID:15568296], which state that adult energy requirements range 20-30 kcal/kg, and 15-30% of the calories should be provided as fat. The guidelines also state that "there is limited clinical benefit when fat content exceeds 30% of nonprotein calories," which results in recommendations that the fat content of parenteral nutrition formulations should not exceed 2.5 g/kg/day. The applicant proposed (b) (4) adult (b) (4) dosing instructions for the product label, (b) (4)

In addition to being an energy source, lipid emulsions are a source of essential fatty acids (fatty acids that can't be synthesized by mammals, due to the absence of enzymes necessary to insert a double bond at the n-3 or n-6 position in the fatty acid chain). There are two essential fatty acids in humans, linoleic acid (LA) and alpha linolenic acid (ALA). Linoleic acid is the precursor of the n-6 polyunsaturated fatty acids, and ALA is the precursor to the n-3 polyunsaturated fatty acids. Essential fatty acid deficiency (EFAD) has a negative impact on the central nervous system, which is particularly important in children, and dermatological manifestations are most prominent in adults. While the dermatological adult manifestations of EFAD are reversible with supplementation, in children the neurological impact of EFAD could have permanent developmental consequences.

Clinolipid is a 4:1 mixture of refined olive oil and soy oil. Currently available "100%" soy lipid emulsions contain substantially higher LA levels than Clinolipid (55-60% of total calories vs. 18.5%). The reviewers evaluated the submitted clinical trials for evidence of EFAD and evaluated the adequacy of the applicant's proposed dosing recommendations for addressing this nutritional need. The applicant noted that a variety of guidelines exist that propose a variable range of recommended EFA intake. There are limited data available upon which to make firm recommendations. The applicant concluded that in adults, the LA intake should range 1-4% of total energy intake and ALA should range 0.2-0.5% of total energy intake. The following chart, reproduced from the CDTL review, was

presented by the applicant to show the amount of Clinolipid that must be administered in order to deliver the high end of % total energy intake for LA recommended in guidelines, i.e., 4%. The calculated volume in adults is less than the total volume that would be delivered to achieve the fat calories needed to meet energy requirements.

Table 5. Calculated Quantities of Clinolipid (ClinOleic) Required to Deliver Adequate Omega-6 Fatty Acids in Adults

Energy Requirements for Average (75 kg) Adult Patient	Daily Omega-6 Fatty Acid Requirement at 1% E	Quantity of ClinOleic Required to Deliver 1% E as Omega-6 Fatty Acid	Daily Omega-6 Fatty Acid Requirement at 4% E	Quantity of ClinOleic Required to Deliver 4% E as Omega-6 Fatty Acid
20 kcal/kg/d (1500 kcal/d)	15 kcal = 1.5 g	40 mL	60 kcal = 6 g	160 mL
25 kcal/kg/d (1875 kcal/d)	18.75 kcal = 1.88 g	50 mL	75 kcal = 7.5 g	200 mL
30 kcal/kg/d (2250 kcal/d)	22.5 kcal = 2.25 g	60 mL	90 kcal = 9 g	240 mL

Source: Applicant, ISE, Table 52, page 196/767

The Clinical reviewers were reassured by the applicant's summary of the data and calculations regarding provision of essential fatty acids to adults; however, they noted the limitations of the available information to firmly establish actual essential fatty acid requirements, in both adults and children, as well as concerns about the limitations of measures used to measure plasma essential fatty acid levels. The reviewers were particularly concerned about the paucity of conclusive data to establish levels needed in children, in whom EFAD could have a devastating effect. In addition, in light of issues identified with actually measuring essential fatty acid levels and defining deficiency, the reviewers questioned whether the clinical trials submitted in support of this application were adequately designed to characterize the risk in both adults and children. Of particular concern was the observation in one study of pre-term infants treated with either Clinolipid or Intralipid (CT 2402/P15/94/G), in which the Holman index (triene/tetraene ratio) in infants treated with Clinolipid deteriorated, instead of improving, as it did on the Intralipid arm. The following table, reproduced from the CDTL review, summarizes this information.

Table 6. Study CT 2402/P15/94/G -- Evidence for persistence of mild of essential fatty acid deficiency in pre-term infants receiving Clinolipid

	Clinolipid n=24		Intralipid N=21	
Holman Index	Baseline	Day 8	Baseline	Day 8
	0.093 ± 0.062 (0.083)	0.112 ± 0.051 (0.085)	0.054 ± 0.033 (0.046)	0.020 ± 0.012 (0.021)
Values are mean ± SD with median in parentheses The triene/tetraene ratio (Holman index) is significantly (p=0.0051) different in the two groups of treatment				

Source: Reproduced from Clinical Review; originally extracted from Text Table 25: Fatty acid profile: Evolution over time and comparison of treatment groups. Page 83 of 2260. Study report CT 2402/P15/94/G

In addition, the Clinical reviewer explored the essential fatty acid data from a pediatric trial that enrolled children ages 2 months to 57 months, using the Mayo Clinic upper limit of normal (identified as the Clinical reviewer as a more modern reference value for EFAD than that used in the submitted trials) as a cut-off for mild EFAD. Using this definition, 7/7 children treated with Clinolipid in the study had mild EFAD, vs. 4/10 children treated with Intralipid.

Finally, the reviewers evaluated the submitted adult trials that included evaluations of n-6 fatty acid. Short term trials showed that 18:2 n-6 decreased in the patients treated with Clinolipid, but increased in the soybean oil treated comparator group patients. In long term studies, the mean levels of 18:2 n-6 increased from baseline to the Month 1 assessment in patients treated with Clinolipid (+0.96 mol%); however, the levels appeared to increase more in the soybean oil comparator arm (+2.54 mol%).

Summary. (b) (4)

(b) (4)

I concur with this recommendation, and I concur with their recommendation to approve the product for adults. I agree it is self-evident that that lipids found in Clinolipid will provide a predictable amount of energy, based on the known amount of kcal associated with a gram of fat infused intravenously. In addition, it is self-evident that Clinolipid contains essential fatty acids. Therefore, technically it is "a source" of essential fatty acids. The applicant's proposed indication doesn't state the amount of essential fatty acids is adequate. Cases of EFAD were not found in the adults enrolled in the clinical trials submitted for review in this NDA. The fact that, by its very nature, it is self-evident the product is a source of energy and fatty acids is the major evidence supporting its approval. Although I concur with inclusion of the two larger, open labeled, randomized, controlled trials identified by the Clinical reviewers, in

Section 14 Clinical Studies of the product label, it should be noted that these trials did not establish superiority or statistical noninferiority of Clinolipid to the lipid emulsion control. However, these trials did provide supportive information that indicated that the lipid emulsion in Clinolipid was bioavailable to provide energy support. Those two trials were conducted in adults. (b) (4)

Based on these review issues, the indication will include two limitations of use and will state:

> CLINOLIPID injection is indicated in adults for providing a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
>
> Limitations of Use
>
> CLINOLIPID injection is not indicated for use in pediatric patients because there is insufficient data to demonstrate that CLINOLIPID injection provides sufficient amounts of essential fatty acids in this population. *[See Use in Specific Populations (8.4)*]
>
> The omega-3:omega-6 fatty acid ratio in Clinolipid injection has not been shown to improve clinical outcomes compared to other intravenous lipid emulsions. *[See Clinical Studies (14)]*

The second limitation regarding 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 component of Clinolipid imparts special qualities that will result in improved clinical outcomes related to anti-inflammatory effects or favorable immune modulatory effects.

8. Safety

In the review of the submitted clinical trials, there was no substantive difference in adverse events qualitatively or quantitatively between the Clinolipid arm patients and the soybean oil comparator arm. 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 necessitated administration of parenteral nutrition.

The most common adverse events that led to death in 386 adults treated with Clinolipid were septic shock (1.3%), subarachnoid hemorrhage (0.5%) and cardiac arrest (0.3%). There was no

obvious imbalance between treatment arms that would suggest that risk was higher with Clinolipid than with the comparator lipid emulsion; however, the trials were small. Similarly, there was no clear difference between arms in non-fatal SAEs. Additional subgroup analyses were conducted to explore for differences in safety between arms in specific risk groups based on the underlying condition (e.g., burn patients, hemodialysis patients, ICU injury or surgery patients, GI surgery patients), and no differences were detected. Again these subgroups were relative small, which limited the ability to draw definitive conclusions.

The reviewers evaluated the trial data for evidence of inadequate provision of essential fatty acids, and development of EFAD. While frank evidence of EFAD was not found, some evidence of differential trends in plasma essential fatty acid levels between Clinolipid and the comparator arm were identified (favoring the soybean oil emulsion comparator). This was discussed above in Section 7 Efficacy. EFAD could lead to devastating neurological sequelae in children and is a serious safety issue for adults as well. (b) (4) See Section 10 below for a discussion of pediatric labeling. It is anticipated that off label use of Clinolipid in children will occur. PMR clinical trials in both the pediatric and adult populations will be required to address the safety concern of essential fatty acid deficiency. These PMR trials will be required under FDAAA to assess a signal of a serious risk of EFAD. (PREA does not apply.) See the end of this section, below, for the approval letter language regarding these trials.

Phytosterols have been implicated as a causative factor of parenteral nutrition associated liver disease. (Xu Z and Li Y-S, Hepatobiliary Pancreat Dis Int, Vol 11, No 6. December 15 2012) Phytosterols are an impurity present in lipid emulsions (which are derived from plants). Phytosterols are plant sterols that are poorly absorbed by the gut when they are ingested as a component of food (estimated 5% bioavailability). In contrast, as a component of parenteral nutrition lipid emulsions, the bioavailability of these phytosterols would be expected to far exceed the exposure achieved in a normal human diet. The submitted trials were too short in duration and inadequately powered to evaluate for risk of developing parenteral nutrition-associated liver disease. No cases were observed. As stated by the CDTL in his review, "PNALD is believed to occur in stages starting with parenteral nutrition associated cholestasis (PNAC), the predominant presentation in infants. As PNAC progresses to PN-associated liver disease (PNALD), the process can lead to a high incidence of morbidity and mortality (Rangel et al. 2012)."

Due to the limitations of the submitted safety database to assess the risks of developing PNALD with Clinolipid, and the fact that Clinolipid contains phytosterols (See Section 3 CMC of this review), the reviewers recommended that the applicant control the levels of the phytosterols in the product, and the approval letter will contain PMR studies to address this product quality issue (See Section 3 CMC). In addition, PMR clinical trials will be required under FDAAA to identify a serious risk of liver injury, which may be related to the presence of phytosterols. See the end of this section, below, for the approval letter language regarding these trials. Because the risk of development of PN-related liver disease is highest in pediatric patients, especially neonates, a 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 completed before

initiating the trial to address liver injury. The applicant will be required to incorporate a phytosterol depleted Clinolipid product for evaluation in this PMR trial. The reviewers discussed the manufacturing issues associated with phytosterol depletion with the CMC reviewers and with an Special Government Employee consultant, Dr. Richard E. Ostlund, MD, who is an nutrition expert knowledgeable in lipid physiology and has experience with commercial manufacturing. These experts reassured the clinical reviewers that manufacturing changes to remove the phytosterol impurity from the product are feasible. The applicant expressed concern about the requirement to develop a phytosterol depleted product for use in this trial. In discussions with the applicant, the FDA clearly articulated to the applicant that the phytosterols are product impurities that have been associated with adverse outcomes. The applicant described challenges they have encountered in developing a phytosterol depleted product, revealing that they have already invested significant effort, predating this NDA, in exploring how to make such a product, including having initiated a nonclinical study of a phytosterol depleted product they have already developed, which is ongoing. The FDA stressed that the product scale that will be required for the PMR is not commercial scale, but clinical trial scale (in volumes appropriate for infant). This is an important safety issue and at this time we have no data to show that conduct of the PMR trial is not feasible. The dates for the study completion and report submission will take into account 3 years of product development time and 2.5 years for trial conduct.

Finally, due to a known serious risk of sepsis and mortality with the use of Clinolipid, the applicant will be required, under 505(o), to conduct a clinical trial in hospitalized patients to evaluate the outcomes of sepsis and mortality. This trial will also assess the requirement for ventilator support and length of stay in the ICU and in the hospital.

The PMR studies that support development of product quality controls for phytosterol levels (PMRs 2085-1, 2085-2, and 2085-3) are listed at the end of Section 3 CMC. One of the PMR studies (PMR 2085-4) in that list is for development of a validated analytical method for measuring phytosterol levels in plasma. The method will be utilized in the PMR clinical trials listed below. The approval letter will state the following regarding the PMR trials required under FDAAA:

> "Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of essential fatty acid deficiency, or assess a known serious risk of sepsis and mortality with the use of Clinolipid (lipid injectable emulsion, USP) 20%, or identify an unexpected serious risk of liver injury in pediatric patients, including neonates, which may be related to the presence of phytosterols.
>
> Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:
>
> 2085- 6 Randomized controlled trial to evaluate the risk of developing essential fatty acid deficiency (EFAD) in pediatric patients, including neonates, receiving either Clinolipid (lipid injectable emulsion, USP) 20% or standard of care

soybean oil based lipid emulsion. 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. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 2085-4.

The timetable you submitted on October 3, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/14
Trial Completion: 09/16
Final Report Submission: 03/17

2085-7 Randomized controlled trial in pediatric patients, including neonates, comparing Clinolipid (lipid injectable emulsion, USP) 20% with a phytosterol-depleted formulation of Clinolipid (lipid injectable emulsion, USP) 20% and another standard-of-care lipid emulsion to evaluate the incidence of liver injury, including either parenteral nutrition-associated liver disease (PNALD) or intestinal failure-associated liver disease (IFALD). This trial should be initiated after the results from PMRs 2085-1, 2085-2, and 2085-6 are available. The phytosterol content of the phytosterol-depleted formulation of Clinolipid (lipid injectable emulsion, USP) 20% should be documented using validated analytical assay methods developed under PMR 2085-1. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 2085-4.

The timetable you submitted on October 3, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 09/16
Trial Completion: 03/19
Final Report Submission: 09/19

2085-8 Randomized clinical trial in hospitalized patients receiving either Clinolipid (lipid injectable emulsion, USP) 20% or other standard-of-care IV lipid emulsions to evaluate clinical safety outcomes of sepsis and mortality. In addition, the trial will evaluate the requirement for ventilator support and length of stay in ICU and hospital.

The timetable you submitted on October 3, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/17
Trial Completion: 10/18

Final Report Submission: 04/19

2085-9 Randomized clinical trial comparing Clinolipid (lipid injectable emulsion, USP) 20% 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 patients receiving chronically-administered total parenteral nutrition (TPN). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 2085-4.

The timetable you submitted on October 3, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 09/14
Trial Completion: 03/17
Final Report Submission: 10/17

9. Advisory Committee Meeting

There was no advisory committee meeting for this application. The product is not an NME.

10. Pediatrics

This NDA did not trigger PREA because olive oil was not considered a new active ingredient (see USP definition of lipid injectable emulsion), the product is not a new route of administration, a new dosage form, a new dosing regimen or new indication. (b) (4) [redacted] The PMHS reviewers also pointed to the safety concern of EFAD in pediatric patients administered Clinolipid as source of calories and fatty acids. In light of the safety concerns associated with administering Clinolipid to children, particularly EFAD, the PMHS reviewers supported a postmarketing requirement under FDAAA to obtain pediatric safety data. They encouraged the review division to consider the heterogeneous pediatric population (ranging from premature infant receiving TPN to a 10 year old on chronic TPN) in developing this PMR. The Clinical reviewers also were concerned about the risk of liver injury in pediatric patients, particularly neonates, which may be related to the presence of phytosterols in lipid emulsions. See the end of Section 8 Safety for the list of pediatric trials that will be required as a condition of approval under FDAAA.

The PMHS consultants worked with the Division to modify the applicant's proposed labeling to remove (b) (4) [redacted]. They recommended retaining the Boxed Warning information regarding preterm infants found in the Intralipid label. They worked with the Division and SEALD to develop a Limitations of Use statement regarding the pediatric population and potential risk for EFAD. Their initial labeling recommendations can be found in their written consult review, and they actively

participated with the pediatric labeling revisions. The PMHS reviewer worked with SEALD to align PMHS recommendations with the most current SEALD recommendations on formatting of pediatric labeling. See Section 12 Labeling below for additional details regarding pediatric labeling.

11. Other Relevant Regulatory Issues

Financial disclosures were submitted for all studies reviewed to support approval. The Clinical reviewer stated in his review that the disclosures were complete and "acceptable".

As the CDTL notes in his reviewer, there were no OSI (Office of Scientific Investigations) inspections of clinical sites requested because of "the historical nature of the clinical studies" submitted for review.

The phytosterol issues safety issues discussed in my review also apply to currently marketed soybean oil products. At the time that Clinolipid is approved, the applicants for the currently marketed lipid emulsion products will be issued a letter informing them that they are required under 505(o) to conduct PMR studies and a PMR trial to assess the serious risk of liver injury in pediatric and neonatal patients, which may be related to the presence of phytosterols. They will be required to develop and validate an appropriate analytical method for determining the individual component phytosterol content in their lipid emulsion product and to test the individual component phytosterol content in all batches of their lipid emulsion product over a 3 year period using the method. Based on the test results, they will establish limits for each of the individual component phytosterols. In addition, they will be required to develop and validate an appropriate analytical method for measuring phytosterol levels in plasma. These validated assay methods for determining phytosterol content in the product and in plasma will support conduct of a randomized, controlled clinical trial that they will be required to conduct under 505(o). This trial will enroll pediatric patients, including neonates, and will compare the fat emulsion product to the same product depleted of phytosterols. Incidence of liver injury, including either parenteral nutrition-associated liver disease or intestinal failure-associated liver disease will be assessed.

12. Labeling

The applicant initially proposed the proprietary name, (b) (4); however, the DMEPA reviewers found the name misleading because (b) (4) The applicant withdrew the name and proposed Clinolipid as an alternative, which both the DMEPA and OPDP reviewers found acceptable.

Recommendations of OPDP reviewers regarding product labeling were incorporated.

The Maternal Health Team from PMHS was consulted to review the labeling for Pregnancy and Nursing mothers, and their recommendations were incorporated. The consultants noted that parenteral nutrition may be used during pregnancy in the setting of hyperemesis gravidarum or if the patient had another serious medical or surgical condition that precluded enteral access to nutrition. Docohexaenoic acid (DHA),an omega-3 fatty acid converted by the body from alpha linoleic acid (ALA), has a role in fetal and infant neurodevelopment.

There are clinical guidelines for the amount of DHA recommended for pregnant and lactating women (200 mg /day). The reviewers conducted a literature search of lipid emulsion use during pregnancy and found a case series in which women were administered soy and soy/safflower oil emulsions. No safety issues attributable to use of the products were identified in the publication. The reviewers noted that the reference product, Intralipid, is labeled as Pregnancy Category C, based on lack of reproductive and developmental toxicology data and lack of human data. The PMHS-MHT team agreed that the applicant's proposed Pregnancy labeling, "Clinolipid should be used during pregnancy only if clearly needed," is appropriate. They acknowledged that Clinolipid has a lower linoleic acid content (omega-6 fatty acid) than Intralipid; however, they pointed to the lack of data on the requirements/benefits of omega-6 fatty acids in pregnancy and for this reason could not comment on the clinical significance of this difference between products for pregnant and lactating women. They didn't recommend specifically noting this difference between products within the Pregnancy section of the product label; however, they recommended that the difference between products should be included elsewhere in the label. Ultimately, the PMHS and Clinical reviewers agreed that Section 8.1 Pregnancy should include the statement, "It is not known whether the administration of Clinolipid 20% to pregnant women provides adequate essential fatty acids to the developing fetus." Their recommendations for revising Section 8.3 Nursing mothers, to align the label with the Proposed Pregnancy and lactation labeling rule, were incorporated.

The PMHS consultants provided labeling revision recommendations (b) (4) Because of the concern about EFAD and its impact in a pediatric population, the PMHS reviewers recommended clearly stating in the indication that the Clinolipid is approved only for adults. They also recommended including a statement in Limitations of Use that the product is not recommended for use in pediatric patients because of the lack of data to support that it provides sufficient essential fatty acids in this population. They recommended that the reference product's Boxed Warning regarding death in preterm infants should be included in the Clinolipid label, and that any proposed references on how to dose preterm infants should be eliminated. They recommended that consideration should be given to describing the risk of aluminum exposure in premature infants, similar to the Intralipid label. This was included in Section 5.8 Aluminum Toxicity and in Section 8.4 Pediatric Use. They recommended specific content for Section 8.4 of the label, including the safety concern regarding thrombocytopenia in neonates described in the reference product label, which were incorporated. However, in the Limitations of Use, "not recommended" was replaced by "not indicated". The applicant preferred the latter because they thought it was a clearer message. PMHS disagreed. The Clinical reviewers discussed this issue with a SEALD reviewer, who stated that there is no currently available definitive guidance on the appropriate wording to address this; however, he considered "not indicated" a stronger and more directive choice of words. For this reason, the Division decided to concur with the applicant's proposed wording.

To address the issues associated with dislodgement of fragments from the administration port, as brought to light by international post marketing reports, the reviewers worked with DMEPA and CDRH to modify the applicant's proposed label to include a new Section, Section 2.1 Use

of an Inline Filter. In addition, to address the concern regarding a specific inlet spike's association with dislodgement of the administration port membrane into the Clinolipid bag, this information was added to Section 2.3 Mixing Guidelines. (See Section 3 CMC above.)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

- Risk Benefit Assessment – I concur with the reviewers that Clinolipid provides intrinsic nutritional value that outweighs the potential risks, and recommend approval of this NDA. Substantial evidence that the new lipid emulsion comprised of both refine olive oil and refined soybean oil, Clinolipid, provides a clinically meaningful advantage over the currently marketed refined soybean oil product was not provided in this NDA. The applicant also did not conduct noninferiority trials designed and powered to establish that Clinolipid is statistically noninferior to the available approved therapy on a specific clinical benefit endpoint. However, humans require energy to sustain life and also require essential fatty acids. Clinolipid is a fat emulsion that provides an objectively documented level of kcal (energy) and contains essential fatty acids. It is self-evident that Clinolipid 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 Clinolipid, given its lower amounts of LA and ALA, relative to the reference product Intralipid, is greatest in children. For this reason the product will not be approved for use in children. Clinical trials will be required under FDAAA to evaluate the risk of EFAD. Clinolipid and soybean oil 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 Clinolipid. Finally, there have been reports of dislodgement of the product's infusion port membrane into the product bag when the port is spiked. These reports are from international sources, where this product is already currently marketed. Because lipid emulsions are in shortage and the human safety impact of this issue can be mitigated by use of an in-line filter, which is already the standard of care for use with lipid emulsion products, the benefit of approving this product outweighs the risk associated with this container issue. A PMR study will be required under FDAA to assess appropriate use of a filter and the ability of the user to spike the administration port. This study protocol will be designed based in part on the review of the applicant's evaluation of the compatibility of available spikes for use with the product in the US (i.e., the pending "Interface Evaluation and Recommendation Report").

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None

- Recommendation for other Postmarketing Requirements and Commitments – See Sections 3 CMC and Section 8 Safety for the list of Postmarketing Required Studies

and Trials that will be required under 505(o). Refer to the approval letter for the four PMCs related to testing the product and setting limits for cholesterol and squalene.

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/s/

DONNA J GRIEBEL
10/03/2013