CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204508Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)2
Application Number(s)	NDA 204508
Priority or Standard	Priority with extension
Submit Date(s)	January 3, 2013
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Division / Office	DGIEP/ODEIII
Reviewer Name(s)	Klaus Gottlieb, MD, MS, MBA
Review Completion Date	September 10, 2013
Established Name	Lipid emulsion (80% soybean oil, 20 % olive oil)
(Proposed) Trade Name	Clinolipid 20%
Therapeutic Class	Lipid emulsion for parenteral nutrition
Applicant	Baxter
Formulation(s)	intravenous
Dosing Regimen	individualized
Indication(s)	Supply of calories and essential fatty acids
Intended Population(s)	Adult, (b) (4)

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that Clinolipid be approved for the following indication:

> Clinolipid is indicated for parenteral nutrition for adults providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated.

In this reviewer's opinion, the product should not be approved for the use (b) (4)

The following or a similar statement should also be placed in the label:

> Clinolipid has a lower content of linoleic acid than Intralipid, the listed drug Linoleic acid is an omega-6 fatty acid which is essential to human health and needs to be provided by the diet or intravenous lipid emulsions. There are insufficient data to determine whether Clinolipid can supply essential fatty acids in adequate amounts, especially in patients who may have increased requirements.
>
> A lower content of omega-6 fatty acids in Clinolipid compared to the listed drug, Intralipid, has not been shown to be associated with beneficial effects upon the immune/inflammatory and oxidative systems and no improved clinical outcomes have been demonstrated.

Alternative recommendations were considered, however, were ultimately thought to be unacceptable.

(b) (4)

1.2 Risk Benefit Assessment

Clinolipid is a safe and effective source of calories. There is a concern that the provision of essential fatty acids in premature newborns may be inadequate, especially if there is a baseline deficit. There are no adequate studies that satisfactorily evaluate the ability of Clinolipid to provide sufficient EFA in pediatric populations whether they have a baseline deficiency or not.
Phytosterols are common to all plant based lipid formulations and are suspected to contribute to PNALD (parenteral nutrition associated liver disease).

A lower content of omega-6 fatty acids (and a concomitantly higher content of omega-3 FA) in lipid emulsions has not been shown to be associated with improved clinical outcomes. Specifically, the applicant concedes that no such benefit has been demonstrated in the comparison of Clinolipid to Intralipid[1].
This is important because there is a firmly established (but unsubstantiated) belief in the nutrition community that such benefits likely exist (see discussion below). This is problematic because prescribers may select Clinolipid over Intralipid for benefits that have not been proven while potentially risking essential fatty acid deficiency given their lower content in Clinolipid compared to Intralipid.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Provided the indication is limited to adults and no claim is being made that Clinolipid is a sufficient source of essential fatty acids (EFA) for pediatric age groups, no Postmarket Risk Evaluation and Mitigation Strategies appear necessary.

[1] This includes biomarkers: “Overall, the data from a number of clinical studies indicate that Clinolipid and soybean oil based lipid emulsions produce similar effects upon the immune/inflammatory and oxidative systems during infusion as part of parenteral nutrition in a large variety of pathological states.” Response to FDA information request. Baxter. 1.11.3 Clinical information amendment. ClinOleic 20% Lipid Injectable Emulsion

1.4 Recommendations for Postmarket Requirements and Commitments

While this reviewer does not recommend [redacted] (b) (4)

1. Adequate Delivery of Essential Fatty Acids and Clinical Outcomes

   A randomized controlled long-term trial comparing Clinolipid with Intralipid in premature newborns, infants, other pediatric patients and adults is required. The adequacy of the provision of EFA should be compared using full FA profiles as they are currently offered by major national reference laboratories. Genetic polymorphisms in the fatty acid desaturase genes (FADS) 1 and (FADS) 2 should be determined in an exploratory analysis to uncover possible subpopulations with altered FA metabolism and increased EFA requirements. The cut-off values for suspected, mild and severe EFA deficiency should be established by a panel of experts prior to the study because the older Holman index cut-off values appear obsolete (see discussion in section 7.1). In addition to the currently used intermediate clinical markers related to the efficiency of nutritional support such as albumin, prealbumin, and anthropometric markers, biomarkers of immune function should be determined[2]. Furthermore, clinical endpoints relevant to all studied populations should be determined. A comprehensive list of possible markers in the population of premature newborns was recently suggested by the Cochrane collaboration "Soy oil based versus alternative lipid emulsions for parenterally fed preterm infants" (Kapoor, Glover, and Malviya 2011). Clinical outcomes for adults have been described in a number of well-conducted trials (Casaer et al. 2011). Further possible endpoints for studies that evaluate clinical outcomes for different populations/clinical settings are suggested in the appendix.

2. Potential Phytosterol Toxicity

   The issue of phytosterols is a safety issue of great public health interest. Plant derived sterols (phytosterols) are contained in all plant derived lipid products but not in those sourced from fish-oil. Phytosterols in an oral diet are generally considered safe, and in fact, can prevent the intestinal absorption of cholesterol, and may therefore have health benefits. In contrast, intravenously administered phytosterols, which reach much higher plasma levels, have been implicated as etiologic factor for Parenteral Nutrition Associated Liver Disease (PNALD) which can be progressive and associated with serious morbidity and mortality.

[2] A comprehensive list of potentially relevant immune function markers is contained in Baxter. 1.11.3 Clinical information amendment. ClinOleic 20% Lipid Injectable Emulsion. See also foot note 1.

Previous clinical studies of varying quality have not been able to isolate phytosterols as a cause because switching between lipid formulations always confounds changes in phytosterol contents with changes in omega-6 fatty acid content. This is relevant because the purported pro-inflammatory qualities of omega-6-PUFA have also been implicated as possible etiologic factor in PNALD. Non-destructive food technologies exist that allow extraction of phytosterols from oils and other plant products that have a high phytosterol content. Extracted phytosterols are then used to enrich, for example, margarine and dietary supplements containing phytosterols (Fernandes and Cabral 2007).
Our expert agrees[3] that such a process or several others could be adapted to produce batches of phytosterol reduced lipid formulations. He also strongly supports the need for a clinical study where reduced-content lipid formulations would be compared to usual-content phytosterol product with otherwise identical composition. The most suitable study population would consist of premature newborns who, as a group, at the highest risk for developing PNALD.

Such a study would help to establish whether phytosterols are a risk factor for the development of PNALD. If so, the small-batch phytosterol process could be scaled up to produce safer lipid emulsions. These changes would, from a regulatory perspective, not create a new drug because phytosterols are considered impurities and not active ingredients

2 Introduction and Regulatory Background

2.1 Product Information

Clinolipid[4] lipid emulsion is a mixture of refined olive oil and refined soybean oil in an approximate ratio of 4:1 (olive:soy), corresponding to an EFA content of 20% of the total fatty acid content. The oils are mixed with small quantities of (b) (4) egg phospholipids and sodium oleate as the (b) (4)r, respectively, together with (b) (4) (b) (4), sodium hydroxide to adjust the pH and Water for Injection (b) (4).

The following table demonstrates the composition of Clinolipid in comparison to Intralipid.

[3] Dr. Richard Ostlund, Washington University in St. Louis, written response to questions by Dr, Klaus Gottlieb, Clinical Reviewer, dated September 8, 2013 (see appendix).
[4] The US-approved name is Clinolipid. In this review the name ClinOleic may appear in sections that quote older data or FDA documents prior to the name change

Table 1.
ClinOleic 20% and Intralipid 20% Lipid Emulsion Qualitative and Quantitative Composition[5]

	ClinOleic 20%	**Intralipid 20% (FK NDA 18-449)**
Component	**Quantity (per 100 mL)**	**Quantity (per 100 mL)**
Olive Oil, NF and Soybean Oil, USP[a]	20 g	--
Soybean Oil, USP	--	20 g
Egg Phospholipids, NF	1.20 g	1.20 g
Glycerin, USP	2.25 g	2.25 g
Sodium Oleate	0.03 g	--
Sodium Hydroxide, NF	for pH adjustment	for pH adjustment
Water for Injection, USP	(b) (4)	qs
Energy content	2000 Kcal/L	2000 Kcal/L
Lipid content (total oil)	0.20 g/mL	0.20 g/mL
pH	6.0-9.0	6-8.9

NF = National Formulary; USP = United States Pharmacopeia
a: A mixture of refined olive oil and refined soybean oil in an approximate ratio of 4:1, respectively. Ratio of refined olive oil to soybean oil is adjusted to achieve a ratio of essential fatty acids (linoleic acid and α-linolenic acid) to total fatty acids of 20%.

The applicant proposes the following indication:

> Indicated for parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Use in Other Jurisdictions

Baxter reports that Clinoleic, the trade name for Clinolipid outside the US, is used in 40 countries around the world. The product was last approved by Health Canada in 2010 with the following indication: Indicated for parenteral nutrition in adults when oral or enteral nutrition is not possible, insufficient, or contraindicated

Historical Background

Of the currently available lipid products for parenteral nutrition Intralipid was the first to gain marketing approval as a 10% solution in 1975 and as a 20% solution in 1981. Over

[5] Baxter ClinOleic 20% Lipid Injectable Emulsion 2.2 Introduction Page 4 of 5

the last 38 years many other products with different compositions have been approved in other jurisdictions but not in the US.

A brief historical overview appears therefore necessary to be able to examine scientific claims for lipid products in context. Early parenteral nutrition in clinical practice (1950s and 60s) started with amino acid and dextrose infusions but it was soon found that providing most of the needed calories as dextrose resulted in fatty infiltration of the liver and essential fatty acid deficiency. This could be prevented by providing a substantial portion of the calories with lipids. Between 1920 and 1960, hundreds of fat emulsions of varying composition were investigated. Lipomul was the first such product available in the United States, However, the adverse effects were serious including chills, fever, nausea, vomiting, and at times dyspnea, hypoxia, and hypotension, and the product was withdrawn from the market after several years[6]. The first nontoxic readily available fat emulsion was developed in Sweden[7] (Intralipid), introduced to the market in 1961 and licensed in the United States in 1975 as a 10% solution and in 1981 as a 20% solution. The initially approved strength, 10%, is now rarely used because adverse events are more likely after administration of a 10% fat emulsion formulation than a 20% formulation because the higher concentration of free phospholipid in the 10% formulation interferes with lipoprotein lipase activity[8] (J. M. Mirtallo et al. 2010).

Over the following years alternatives to the pure soybean oil based fat emulsions have been developed and categorized in a recent ASPEN (American Society for Parenteral and Enteral Nutrition) position paper as follows (Vanek et al. 2012):

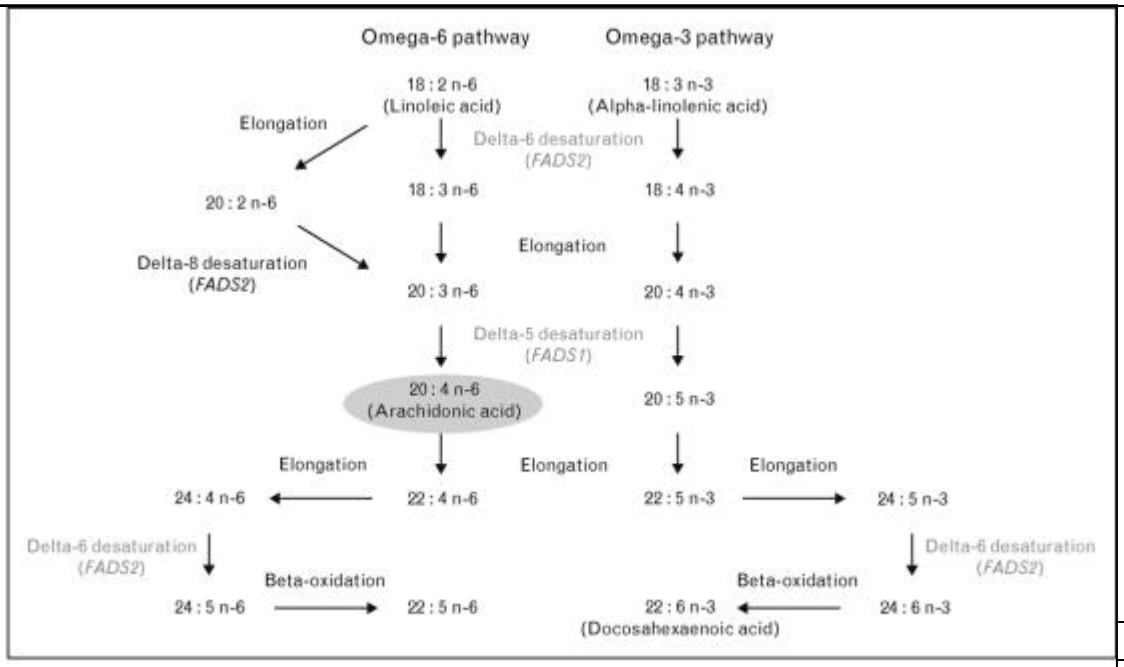
- Generation 1 (1961): long-chain neutral TG (triglyceride) soybean oil (SO)
    - 85 % omega-3, omega-6, omega-9 (nonessential)
- Generation 2 (1984): SO:MCT[9]=50:50
    - To reduce omega-6 content
- Generation 3 (1990's): OO[10]:SO=80:20
    - Further decrease of omega-6 content
- Generation 4 (recent): IV lipids containing fish-oil
    - Increase content of omega-3

Linoleic acid, while an essential fatty acid is also an omega-6 FA that is considered proinflammatory (explained below) by many nutrition practitioners. For example, the authors of an ASPEN position paper state that "…patients could potentially have better

[6] Lipomul was a cottonseed oil emulsion which in many patients produced fever, coagulation defects and jaundice. These problems were due to a nonextractable toxic substance in the cottonseed oil and the emulsifying agent, which damaged erythrocytes causing aggregation. Deitel, Mervyn, and Victor Kaminsky. "Total nutrition by peripheral vein—the lipid system." Canadian Medical Association Journal 111.2 (1974): 152.
[7] After many years of trial and error, Wretlind had found that an emulsion prepared from soy-bean oil and egg yolk phospholipids, used as an emulsifier, could be safely infused (Vinnars and Wilmore 2003).
[8] Exceeding the capacity of the lipoprotein lipase leads to hypertriglyceridemia and, depending on the degree, other effects such as acute pancreatitis, cholestasis, and increased risk of infection
[9] Soybean oil : Medium chain triglycerides
[10] OO: Olive oil

clinical outcomes when receiving one of the alternative IVFEs to diminish the intake of the potentially proinflammatory ω-6 fatty acid—linoleic acid—which comprises more than 50% of the fatty acid profile in SO." The statement "could potentially have better outcomes" acknowledges that there are to date no outcome studies that prove these benefits for lipid formulations that have a lower omega-6 fatty acid content.

The metabolism of omega-6 and omega-3 FA in relationship to arachidonic acid production is described in the following image. The omega-6 oxidation pathway leads to the formation of arachidonic acid, the parent compound for prostaglandins, prostacyclins and leukotrienes, most of them with proinflammatory activity.



Modified with permission [1].

Physiologic Chemistry of Lipid Emulsions and Relevance to Dosing

Intravenous fat emulsions (IVFEs) are designed to be similar to endogenous chylomicrons. They are cleared by the enzyme lipoprotein lipase, which hydrolyzes triglycerides, releasing free fatty acids, glycerin, and phospholipids. Three factors affect the plasma clearance of IVFEs: (1) phospholipid content (10% vs. 20% IVFE), (2) particle size, and (3) infusion rate. The phospholipid content of the 10% and 20% formulations is the same; therefore, there is proportionally more free (not participating in emulsifying the oil) phospholipid available in the 10% formulation. Free phospholipids interfere with lipoprotein lipase activity, thereby decreasing IVFE clearance and increasing the potential for AEs. Clearance of 20% IVFE is faster than that of 10% IVFE due to its relatively lower concentration of free phospholipids and its larger particle size. The IVFE infusion rate is the third factor determining plasma clearance of IVFEs. Administration of an IVFE to adults at a rate >2.5 g lipid/kg/day may result in an excessive lipid load. Once it is cleared from the plasma by various tissues, not all fat is

oxidized. The fate of free fatty acids released from IVFE is dependent on its component oil. Long-chain triglycerides (LCT) require a carnitine-dependent co-transport system in order to be taken up by mitochondria and subsequently oxidized. This process involves the conversion of the LCT into acyl coenzyme A (CoA), which is not sufficiently water soluble to pass into the mitochondria. Carnitine picks up the acyl component of acyl CoA (acylcarnitine) and transports it across the mitochondria matrix where the acylcarnitine equilibrates with CoA to form acyl CoA within the mitochondria, thereby completing its transport.

The phospholipid emulsifier provides stability to IVFEs by functioning as both a mechanical and electrical barrier. Phospholipid molecules have a polar (hydrophilic) and a nonpolar (lipophilic) end, and they orient themselves so as to create the oil-water interface. The polar ends toward the water exist in the neutral environment primarily in dissociated states, resulting in an anionic charge that creates a repulsive force, preventing the fat particles from coalescing. If these forces were not present, eventually the emulsion would fail, the lipids would coalesce, and the IVFE, if administered, would produce fat emboli. Since the basis of the electrical barrier is the anionic charge, stability of the IVFE may be compromised by divalent cations (magnesium and calcium), trivalent cations (iron), or an acid pH (especially at pH <5).
In most cases, even in the presence of these agents or conditions, complete destabilization of the emulsion takes time, the length being dependent on the concentration of the chemical and environmental conditions such as extreme temperatures. Over this time, the particle size of the emulsion may increase, which might result in excessive uptake by the reticuloendothelial system (RES), causing a functional impairment in this system's ability to clear bacteria (J. M. Mirtallo et al. 2010).

Clinolipid

Clinolipid is an intravenous lipid formulation which consists of 80% olive oil and 20% soybean oil. Further details about the chemical composition can be found in the CMC section. The listed drug is Intralipid which consists of 100% soybean oil. Clinolipid alone, or as part of a parenteral nutrition program, is intended to treat 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.

The benefits of Clinolipid are described by the applicant is as follows:

> Clinolipid is a lipid emulsion indicated for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Clinolipid provides an adequate supply of lipids for energy and essential fatty acids for patients requiring parenteral nutrition.

The product under review, Clinolipid, falls into the Generation 3 category above and has decreased omega-6 fatty acid content.

The applicant in this NDA makes no explicit labeling claims that patients receiving Clinolipid have better clinical outcomes than those who receive entirely soybean oil based formulations or that the decreased omega-6 content is beneficial. However, claims of a similar nature can be found in the drug labels of other jurisdictions, for example, Israel: “The moderate content of essential fatty acids (EFA) probably facilitates their use and improves the patient’s status with respect to higher EFA derivatives, and corrects EFA deficiency”. Higher EFA derivatives include prostaglandins, leukotrienes and others, which are collectively considered to be proinflammatory mediators.

While convincing evidence for a beneficial effect of decreased omega-6 content is lacking (see below), nutrition practitioners seem to think that a benefit probably exists, and this assessment is also reflected in the previously cited ASPEN position paper (Vanek et al. 2012). This is relevant because prescribers may assume that a benefit indeed exists unless it is pointed out in the label that a clinical benefit of lower omega-6 content has not been demonstrated.

Rationale for Parenteral Nutrition

Nutrients required by humans can be supplied by either endogenous mobilization/breakdown from tissue stores or through exogenous sources (i.e., diet). When energy is not available from the diet, cells can produce energy through catabolism of lipids, carbohydrates, and proteins (amino acids); however, catabolism of these compounds leads to loss of tissue mass that can eventually lead to loss of tissue functions.

Nutrient delivery is particularly important in malnourished patients who have lost body mass and suffer from compromised tissue functions (lack reserves to mobilize nutrients for maintenance and recovery of cell integrity). Nutrients can be delivered via the oral or gastrointestinal (GI) routes (enteral nutrition), or via the intravenous (IV) route (parenteral nutrition).

The parenteral route may be the only or most important route for nutrient delivery in patients with GI dysfunction who lack the capacity to absorb adequate nutrients for maintenance or recovery of tissue mass and function. Gastrointestinal dysfunction is common in patients with intrinsic GI disease (e.g., motility disorders, inflammatory bowel diseases, short gut syndromes) and in patients with GI dysfunction that results from non-GI diseases (e.g., burns, sepsis, shock, multiple trauma).

The primary goals of parenteral nutrition are to supply patients with adequate energy and essential nutrients. Energy is supplied using a mixture of carbohydrate (primarily glucose) and lipids. Lipids have the highest energy content and serve as the primary source of cellular energy. Lipids have also been shown to decrease the requirement for high-dose glucose, which contributes to hyperglycemia in critically ill, diabetic, and other stressed patients. Hyperglycemia has been associated with increased morbidity and

mortality in these patient groups. Lipids also supply the patient with essential fatty acids (EFA), (fatty acids that the patient cannot synthesize). The EFA are required by cells for optimal structure and function of cell membranes, cell division (requires lipid for membrane synthesis), and production of cell signaling and regulatory molecules.

Although lipids can be supplied as oils during enteral feeding, lipids must be emulsified into small particles for use during parenteral nutrition. The emulsification process suspends the fatty acids (in the form of triglycerides) into small chylomicron-like particles that can safely be delivered into the vascular system. The size of the lipid droplets is critical: because of mechanical filtration, larger-size fat globules (>5 μm) can be trapped in the lungs [Driscoll 2007]. The first commercialized lipid emulsions were based upon soybean oil (a rich source of the essential fatty acid, linoleic acid). More recent lipid emulsions are based upon mixtures of oils that are felt to possess better physiologic fatty acid profiles.

Important controversies in the field of parenteral nutrition

While there are many areas where the value of parenteral nutrition is not debated, for example, in patients who have permanently lost their ability to tolerate oral nutrition (such as in short gut syndrome), controversies exist for the setting where it is most frequently employed, the intensive care unit.
Recent studies on the optimal modalities to feed patients during the ICU stay show divergent results. The level and the timing of energy provision is a critical issue, associated with the clinical outcome. These results challenge the clinical relevance of the recent guidelines issued by American, Canadian and European academic societies (Singer and Pichard 2013).
A large trial with 4640 randomized patients (Casaer et al. 2011) showed that there was no significant difference in mortality between late initiation and early initiation of parenteral nutrition among patients in the ICU who were at risk for malnutrition, despite the use of early enteral feeding plus micronutrients in a protocol that prevented hyperglycemia. However, withholding of parenteral nutrition until day 8 was associated with fewer ICU infections but a higher degree of acute inflammation as measured by C-reactive protein. Late initiation of parenteral nutrition was also associated with a shorter duration of mechanical ventilation and a shorter course of renal-replacement therapy, a shorter ICU stay despite a slight increase in hypoglycemic episodes, a shorter hospital stay without a decrease in functional status, and reduced health care costs.
These results were supported by an observational study conducted in 226 intensive care units from 29 countries and over 2900 patients. The authors concluded that the supplemental use of parenteral nutrition may have improved provision of calories and protein but was not associated with a clinical benefit (Kutsogiannis et al. 2011).

Relevance of differences in content of polyunsaturated fatty acids

Numerous investigations have failed to produce a clear picture of the immunologic characteristics of the most commonly used soybean oil–derived lipid emulsions, although their high content of n−6 polyunsaturated fatty acids (PUFAs) has been considered a drawback because of their potential proinflammatory potential. This concern initiated the development of emulsions in which part of the n−6 FA (fatty acid) component is replaced by less bioactive FAs, such as coconut oil (rich in medium-chain saturated FAs) or olive oil (rich in the n−9 monounsaturated FA oleic acid). Another approach has been to use fish oil (rich in n−3 PUFA), the FAs of which have biological activities different from those of n−6 PUFAs (Wanten and Calder 2007).

While possible advantages of omega-3 rich lipid solutions (i.e., those that contain no or little soybean oil) in patients at highest risk for infectious complications are widely believed and have achieved level D recommendation[11] status in certain guidelines (McClave et al. 2009) no such advantages have been demonstrated in a large comparative randomized trial (Umpierrez et al. 2012) that was considered 'well-conducted' but perhaps not definitive by an accompanying editorial (Freire 2012).

2.2 Tables of Currently Available Treatments for Proposed Indications

Lipid products for parenteral infusion come in different strengths but 20% formulations are the most widely used. Currently licensed products and strengths in the US are 10% (Intralipid 10% with therapeutic equivalents Liposyn III 10% and Nutrilipd 10%), 20% (Intralipid 20%, no equivalents) and 30% (Intralipid 30% with therapeutic equivalent Liposyn III 30%). Of the licensed products only Intralipid and Liposyn are currently available, both of them affected by shortages (Research 2013). The mentioned products are 100% soybean oil based. Clinolipid is a product that contains 20% soybean oil and 80% olive oil.

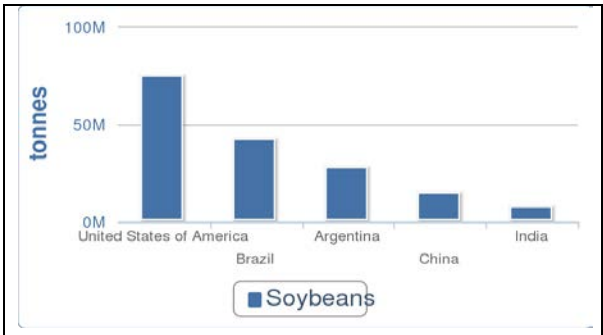
Company	Product	Availability and Estimated Shortage Duration	Related Information	Shortage Reason (per New Legislation-FDASIA)*	Date Updated
Hospira Inc.	10%; 250 mL (NDC 0409-9790-02)	Hospira continues to investigate manufacturing process improvements.	Shortage per Manufacturer: Quality improvement activities	Requirements related to complying with good manufacturing practices	**Reverified** 5/20/2013
	10%; 500 mL (NDC 0409-9790-03)				

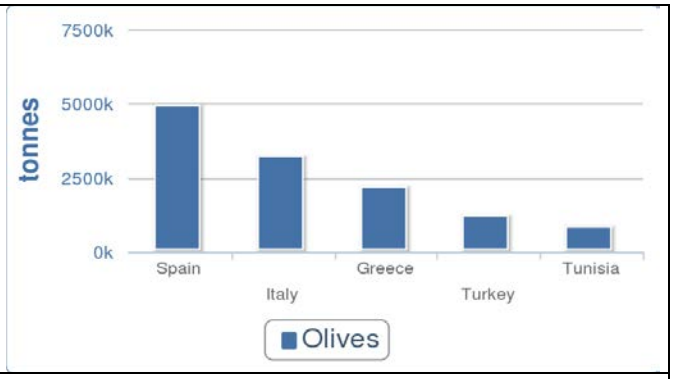
[11] Level D : Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

	20%; 250 mL (NDC 0409-9791-02)				
	20%; 500 mL (NDC 0409-9791-03)				
	30%; 500 mL (NDC 0409-6892-03)				
Baxter (Intralipid Emulsion)	Intralipid 20% Emulsion, 100 mL (NDC 00338-0519-48)	Back-ordered Baxter has the following Intralipid 20% emulsions on allocation and is working to increase production to meet US market demand. All orders must be made directly with Baxter's Center for Service by calling 1-888-229-0001.	N/A	Demand increase for the drug	**Reverified** 5/7/2013
	Intralipid 20% Emulsion, 250 mL (NDC 00338-0519-02)				
	Intralipid 20% Emulsion, 500 mL (NDC 00338-0519-03)				
	Intralipid 20% Emulsion, 1000 mL (NDC 00338-0519-04)				
	Intralipid 30% Emulsion, 500 mL (NDC 00338-0520-03)	Intralipid 30% Emulsion Available			

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients are olive oil and soybean oil. The US is the largest producer of soybeans. The 5 largest producers of olives and olive oil are in Europe and North Africa. Bottle necks and shortages for the finished drug product are not related to problems with supply of active ingredients but manufacturing issues (see table above).





Average 1991-2011 Retrieved from http://faostat3.fao.org

2.4 Important Safety Issues With Consideration to Related Drugs

Adequate amounts of essential fatty acids

Linoleic acid (LA) and alpha-linolenic acid (ALA) cannot be synthesized by humans and are therefore essential components of the diet. The requirements for LA are approximately ten times higher than those for ALA and LA can therefore be considered the more important of the two. The LA content of Clinolipid (80% olive oil-20% soybean oil) is approximately 20% of the LA content of Intralipid (100% soybean oil). While this amount may be satisfactory in many circumstances, European guidelines caution that "when prescribing lipid emulsions [for preterm infants] the different LA content of the available lipid emulsions needs to be taken into account" (Koletzko et al. 2005) . The topic of adequate supply of essential fatty acids (EFA) will be reviewed in more depth in Section 7 (Safety).

Phytosterols are plant sterols that are contained in all plant derived lipid formulations. They have been implicated in parenteral nutrition associated liver disease. This topic will be more fully discussed in the Safety section.

Other safety issues relate to the content of leachable organic compounds that could enter the lipid formulation from the [redacted] (b) (4) container bag and the content of elemental impurities in the lipid solution.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This is a 505(b) 2 application with Intralipid as listed drug. A presubmission meeting was held under PIND 074881 on July 13, 2011.

A section from the FDA meeting minutes is quoted below because it is relevant to the concerns this reviewer has, especially regarding the adequate provision of EFAs:

> It is possible that the data you have collected to date could demonstrate the safety and efficacy of ClinOleic as a source of calories and essential fatty acids. It is not clear if an adequate and well-controlled clinical trial has been performed with ClinOleic that can demonstrate effectiveness or a clinically meaningful benefit, or whether such trials are feasible. Further discussion both internally and with Baxter will be needed to help us identify the most suitable approach.
> It is possible that a 505(b)(2) application that relies on the Agency's previous findings of safety and/or effectiveness for a listed drug (e.g., Intralipid) could be submitted (see our response to Question 3 below). However, you would also need to provide evidence that ClinOleic can provide adequate essential fatty acids to patients receiving longer term parenteral nutrition. In addition, you will need to submit justification, with supportive data, that the lipid composition and emulsion formulation of ClinOleic would not pose new safety concerns over currently available IV lipid emulsions. At this time, it is not clear if the data you have collected to date will be sufficient for this purpose or if additional studies(e.g., PK/PD) are warranted.

The 505(b)2 application pathway can be considered appropriate because Clinolipid differs from Intralipid substantially only by a lower content of linoleic acid, a omega-6 essential fatty acid ("different strength"). A different strength does not trigger PREA (Pediatric Research Equity Act) provisions.

2.6 Other Relevant Background Information

The following table contains label information from other jurisdictions[12]. Please note that some labels limit the population to adults and/or do not contain "provision of essential fatty acids".

[12] Sources: UK http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1361852005461.pdf Canada http://www.baxter.ca/en/downloads/product_information/ClinOleic_PM_EN.pdf Australia: http://www.baxterhealthcare.com.au/downloads/healthcare_professionals/cmi_pi/clinoleic_pi.pdf

Comparing ClinLipid (Clinoleic) Labels			
	UK/ Europe	**Australia**	**Canada**
Indication	Indicated as a **source of calories and essential fatty acids** for patients requiring parenteral nutrition.	Parenteral nutrition when oral or enteral nutrition is impossible, insufficient or contra-indicated.	Indicated for parenteral nutrition in adults when oral or enteral nutrition is not possible, insufficient, or contraindicated
		Proposed US Indication: Indicated for parenteral nutrition providing a **source of calories and essential fatty acids** when oral or enteral nutrition is not possible, insufficient, or contraindicated	
Pivotal Studies	None listed	CT 2402/P14/93/F and CT 2402/P15/94/G	C89 CSW 6/3 08F and C89 CSQW 6/3 10F
Population/ duration		1- 9 y o for 2 months, preemies for 8 days	17 – 75 yrs for 22 days, 47 – 75 yrs 145 – 202 days
Endpoints		fatty acids in plasma phospholipids	Nutritional criteria, triglyceride levels Plasma phospholipids fraction, Clinical tolerance, Biological tolerance (hepatic and lipid parameters, haematology, phosphorus and calcium homeostasis, biochemical parameters)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No Refusal-To-File-issues were raised at the filing meeting. However, this application relies on a multitude of disparate studies with small numbers of patients which were conducted, with the exception of one, in the late 1980s and early 1990s, trying to answer a plethora of different questions (see Table in section 5.2). Many of the studies have only a rudimentary statistical analysis plan and try to answer questions of "comparability" (equivalence or non-inferiority) by considering non-significant differences by p-value evidence of "no difference". This approach is not valid because study sizes could be made arbitrarily small to cause a type II error thus evading the detection of

significant differences even if they exist. There is only one short-term non-inferiority study. Pooling of these studies appears problematic or impossible. However, the question “Is ClinOleic an adequate source of calories and essential fatty acids” can be satisfactorily evaluated in this submission (see Review Strategy 5.2).

3.2 Compliance with Good Clinical Practices

No deficiencies identified.

3.3 Financial Disclosures

Financial disclosures were submitted for all studies. They appear complete and are acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are a number of CMC issues which at the time of the submission of this review are still awaiting successful resolution

1. Missing information about certain leachables that could enter lipid formulation from the (b) (4) container.
2. The integrity of the container closure system in regards to microbiological contamination
3. Establishment of a validated analytical method to determine phytosterol content in production lots
4. Content of elemental impurities
5. Resiliency testing for the (b) (4) bag
6. Detachment of the sterile blue membrane in CLINOLEIC 20% emulsion was observed by Health Canada after spiking the administration port. This could potentially result in particulate matter entering the emulsion.

For details please refer to the CMC review.

4.2 Clinical Microbiology

See issue 2. above. The integrity of the container closure system in regards to microbiological contamination

4.3 Preclinical Pharmacology/Toxicology

No concerns or issues.

4.4 Clinical Pharmacology

No concerns or issues.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The applicant provided 31 studies and clinical trials. A complete listing is in the appendix. Of the 9 controlled studies comparing Clinolipid to Intralipid in adult patients only three are long-term studies, the rest have a duration of 5 days. Of the three long-term studies one had only three treated patients, reducing the number of relevant studies for the efficacy analysis to two.

Controlled Studies Comparing Clinolipid to Intralipid in Adult Patients								
Efficacy and Safety	C 88 CSW 6/3 01 F	Evaluate short-term tolerability and effect on membrane and fatty acid profiles	Single center, randomized, open label, active control	ClinOleic versus Intralipid 2.45 g/kg/day IV	20 planned 7 treated 4 ClinOleic, 3 Intralipid	ICU patients following abdominal surgery	5 days	Complete; Full
Efficacy and Safety	C 88 CSW 6/3 02 F	Evaluate short-term tolerability and effect on membrane and fatty acid profiles	Single center, randomized, open label, active control	ClinOleic versus Intralipid 1.3 g/kg/day IV	20 planned 27 treated 15 ClinOleic, 12 Intralipid	ICU patients following gastrointestinal surgery or multiple trauma	5 days	Complete; Full
Efficacy and Safety	C 88 CSW 6/3 05 F	Evaluate short-term tolerability and effect on membrane and fatty acid profiles	Single center, randomized, open label, active control	ClinOleic versus Intralipid 2.3 g/kg/day IV	16 planned 20 treated 11 ClinOleic, 9 Intralipid	ICU patients following gastrointestinal surgery or multiple trauma	5 days	Complete; Full
Efficacy and Safety	C 88 CSW 6/3 06 F	Evaluate short-term tolerability and effect on membrane and fatty acid profiles	Single center, randomized, open label, active control	ClinOleic versus Intralipid 2.3 g/kg/day IV	20 planned 20 treated 11 ClinOleic, 9 Intralipid	ICU patients following gastrointestinal or vascular surgery, multiple trauma or burns	5 days	Complete; Full
Efficacy and Safety	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) IV	48 planned 48 treated 24 ClinOleic, 24 Intralipid	Hospital patients requiring total parenteral nutrition	15 days to 6 months	Complete; Full

Efficacy and Safety	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 IV	50 planned 22 treated 12 ClinOleic, 10 Intralipid	Hospital or ambulatory patients requiring supplemental parenteral nutrition	26 days to 1 year	Complete; Full
Efficacy and Safety	C 90 CSW 6/3 11 F	Evaluate efficacy and safety with long-term use	Single center, randomized, open label, active control	ClinOleic versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day) IV	12 planned 3 treated 2 ClinOleic, 1 Intralipid	Hospital patients requiring total parenteral nutrition	15 days to 6 months	Complete; Full
Efficacy and Safety	C 91 CSW 6/3 13 F	Evaluate short-term tolerability	Single center, randomized, open label, active control	ClinOleic versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day) IV	20 planned 24 treated 13 ClinOleic, 11 Intralipid	Hospital patients requiring total parenteral nutrition	5 days minimum	Complete; Full
Efficacy and Safety	CT 2402/P24/03/C	Evaluate short-term (5 days) efficacy and safety	Multicenter, randomized, double-blind, active control	ClinOleic versus Intralipid 1 g/kg/day IV	200 planned 200 treated 100 ClinOleic, 100 Intralipid	Hospital patients requiring parenteral nutrition for at least 50% of needs	5 days	Complete; Full

5.2 Review Strategy

The applicant desires an indication for Clinolipid as “a source of calories and essential fatty acids” and the review team has decided to focus the review on these topics. Many of the submitted studies in this NDA were, judging by their primary objectives, apparently chiefly conducted to evaluate biomarkers that would show a possible advantage of Clinolipid over other lipid products in the area of inflammation and immunity, a major research focus in the 1990s when most of these studies were commissioned (the following table provided by the applicant contains the comparative trials broken out by parameter of interest).

Summary of Efficacy-Related Findings for ClinOleic Studies in Adult Patients		
Parameter	Studies that Evaluated Parameter	**Overall Results**
Albumin	CT2402/P24/03/C CT2402/P20/96/I CT2402/P17/95/UK CT2402/P22/00/F	Similar to comparator
Transthyretin	CT2402/P24/03/C	Similar to comparator
Nitrogen Balance	C88CSW 6/3 02F	Similar to comparator
Anthropometrics	C89CSW 6/3 08F CT2402/P17/95/UK CT2402/P24/03/C CT2402/P20/96/I C89CSW 6/3 10F	Similar to comparator
Essential Fatty Acid Deficiency	C89CSW 6/3 08F CT2402/P18/95/F	No essential fatty acid deficiency (this reviewer disagrees with this conclusion)

Triglycerides	C88CSW 6/3 02F C89CSW 6/3 08F C88CSW 6/3 01F C89CSW 6/3 10F C88CSW 6/3 05F CT2402/P17/95/UK C88CSW 6/3 06FCT 2402/P18/95/F C91CSW 6/3 13F CT2402/P20/96/I CT2402/P24/03/C CT2402/P22/00/F	Similar to comparator
Fatty Acids	C88CSW 6/3 02F CT2402/P19/96/G C88CSW 6/3 01F CT2402/P21/96/S C88CSW 6/3 05F CT2402/P18/95/F C88CSW 6/3 06F CT2402/P22/00/F	Oleic acid increased with ClinOleic; linoleic acid increased with comparator lipids; ClinOleic maintained better synthesis of longer fatty acid derivatives
Inflammation	CT2402/P21/96/S CT2402/P18/95/F CT2402/P22/00/F	ClinOleic maintained higher IL-2 levels and lower ESR
Oxidation	CT2402/P19/96/G CT2402/P22/00/F	ClinOleic was associated with improved vitamin E status and lower homocysteine levels
Cullen's Index	C88CSW 6/3 01F C88CSW 6/3 06F C88CSW 6/3 05F	Similar to comparator
Adapted from applicant's presentation at preNDA meeting July 13, 2011		

Plant derived intravenous lipid products mainly contain C-18 to C-20 length fatty acids and regardless of their provenance, soybean oil or olive oil, are calorically equivalent in the laboratory. If the same amounts are administered, the same amount of calories will be supplied. However, whether the same amount is actually being given depends on a number of factors, such as tolerability, or incidence of adverse events.

If product A is associated with adverse events or other tolerability problems that lead to discontinuation of the product, the success in the administration of calories is not the

same as product B that does not have these adverse events. While the applicant has failed to design their “nutritional equivalence” studies as non-inferiority studies, this is, in this reviewer’s opinion, not a major issue because at least in-vitro caloric equivalence can be assumed a priori without doing clinical studies. Then it just remains to be shown that the applicant’s product does not, for whichever reason, lead to a higher discontinuation rate.

Clinical caloric equivalence can therefore rely on the much larger database of clinical tolerability data both provided by the applicant and in the published literature (“safety database”). The following is a list of possible problems that could interfere with the provision of calories in clinical practice (even for lipid formulations whose active ingredients are chemically equicaloric). In the absence of these problems two lipid formulations that are as similar in fatty acid composition as Clinolipid and Intralipid can be considered to be equivalent in the provision of calories also in clinical practice.

Some safety problems which would interfere with the provision of calories could be:

- The lipid formulation may contain pyrogens or toxins that interfere with tolerability
- The size of the artificial chylomicrons is too large causing adverse events
- The lipid emulsion is unstable and the chylomicrons coalesce to larger aggregates over time
- The lipid composition is poorly cleared from the circulation and causes hypertriglyceridemia necessitating dose reductions
- The lipid formulation causes other adverse events requiring discontinuation or dose reduction

It does not appear that any of the first three points are current concerns. Please see the CMC review for a full discussion. In consequence of the above, the review of efficacy is to a large extent also a clinical safety evaluation.

Table 1

Energy Supplied by ClinOleic and Intralipid Lipid Emulsions				
	ClinOleic		**Intralipid**	
Component	**Mass Concentration (g/L)**	**Energy Concentration (kcal/L)**	**Mass Concentration (g/L)**	**Energy Concentration (kcal/L)**
Oils	200	1800[a]	200	1800[a]
Egg phospholipids	12	108[a]	12	108[a]
Glycerin	22.5	90[b]	22.5	90[b]
Sodium oleate	0.3	2.7[a]	0	0
Total energy		**2000.7**		**1998**

[a] The energy content of lipids is 9 kcal/g.
[b] The energy content of carbohydrates is 4 kcal/g.

Applicant's Table 5 in ClinOleic 20% Lipid Injectable Emulsion 2.7.2 Summary of Clinical Pharmacology Studies , page 22 of 24

Safety and efficacy analysis also intersect in the assessment of the adequate delivery of essential fatty acids. A lipid product that cannot supply an adequate amount of fatty acids may both lack efficacy and be considered unsafe in certain circumstances.

From an efficacy perspective an intravenous lipid emulsion for clinical use should be expected to supply adequate amount essential fatty acids to prevent the development of fatty acid deficiency. From a safety point of view an intravenous lipid product should be able to restore essential fatty acids stores when these are low or depleted and keep up with long-term requirements so that essential fatty acid deficiency does not arise while patients are on that product.
The above illustrates that it is hard to separate the aspects of safety and efficacy in the case of provision of essential fatty acids. This topic is discussed more fully in the subsequent sections.
It is important that prescribers can be confident that the administration of a specific lipid emulsion can replenish essential fatty acid stores in patients who have preexisting EFAD using the usually tolerated or recommended infusion amounts, especially in premature infants who rely on EFA for their neurological and overall development.

5.3 Discussion of Individual Studies/Clinical Trials

Of the 9 controlled studies comparing Clinolipid to Intralipid in adult patients only three are long-term studies, the rest have duration of 5 days. In the long term trial C 90 CSW 6/3 11 F only three patients were treated. We will therefore only review the following two adult trials in detail in this document followed by two pediatric trials (see Section 6.1.7):

Adult	Patients	Age (years)	Duration	Endpoint	Results
Study 1 C89 CSW 6/3 08F	48	17-75	mean 22 days	anthropometric measures	No significant difference
Study 2 C89 CSQW 6/3 10F	22	32-81	mean 202 days	anthropometric measures	No significant difference

6 Review of Efficacy

Efficacy Summary

Clinolipid is an adequate source of calories from fat for adults and children based on its similar fatty acid content compared to Intralipid and based on the results of clinical studies. However, (b) (4)

(b) (4)

6.1 Indication[13]

Of the numerous studies that were furnished by the applicant, the following two adult long-term studies were considered adequate and well controlled to support a claim of adequate provision of calories from fat:

[13] The unusual nature of this NDA makes it difficult to strictly adhere to the template outline for an NDA review. This first section is meant to be an "Integrated Review of Efficacy as it pertains to the Indication".

Highlights of study C89 CSW 6/3 08F in adults	
Primary Endpoints	**Results**
Nutritional criteria	Improvement of anthropometry and biological nutritional status (albumin, total protein, gamma globulin) in both groups (difference not significant)
Plasma triglyceride levels	No significant differences in plasma triglyceride levels.
Plasma phospholipids fraction	Significant difference between the two groups ($p < 0.0001$) with regard to the change in oleic acid (C18:1n-9) and linoleic acid (C18:2n-6): - Increase in oleic acid (non-essential) and decrease in linoleic acid (EFA) in CLINOLEIC group - Decrease in oleic acid and increase in linoleic acid in refined soybean oil lipid emulsion group.

Study 1 (adult, C89 CSW 6/3 08F) was a randomized, open-label, multi-center study conducted between February 1990 to December 1992. Forty eight (48) patients, aged 17 to 75 years, requiring prolonged (≥15 days, mean 22 days) exclusive parenteral nutrition (TPN) were enrolled and randomized into the study. Nutritional efficacy was assessed by anthropometric indices (body weight, arm circumference, skin-fold thickness); biomarkers of protein metabolism (total protein, albumin) and lipid metabolism. Safety of the lipid emulsions was assessed by biomarkers of hepatobiliary function, with abdominal ultrasound; hematologic, renal and endocrine laboratory parameters, pancreatic enzymes, and electrolyte status.
Differences between treatment groups for anthropometric criteria (body weight, arm circumference, and skin fold thickness) were not statistically significant and showed comparable improvement for both groups,
Mean total protein and albumin increased similarly in both groups; differences between treatment groups were not statistically significant. Adverse events and laboratory safety data were comparable for the two lipid groups. The observed increase in oleic acid (non-essential) and decrease in linoleic acid (EFA) in the Clinolipid group and mirroring changes in the Intralipid group consisting of a decrease in oleic acid and increase in linoleic acid were expected.

Highlights of study C89 CSW 6/3 10F in adults	
Primary Endpoints	**Results**
Clinical tolerance	Anthropometric criteria (weight, mid-arm circumference, triceps skin fold) showed similar improvement in both groups.
Biological tolerance (hepatic and lipid parameters, hematology, phosphorus and calcium homeostasis, biochemical parameters)	Results for lipid parameters (e.g., plasma triglycerides, total cholesterol, HDL cholesterol, phospholipids) showed no significant differences between groups. Results for hepatic parameters (e.g., AST, ALT, alkaline phosphatase, GGT) showed no significant differences between groups. No significant differences between groups in haematology, plasma proteins, phosphocalcic homeostasis or biochemical parameters.

Study 2 (adult, C89 CSQW 6/3 10F) was a randomized, open label multicenter study conducted from February 1990 to September 1993 and enrolled 22 patients aged 32-81 years who required long-term parenteral nutrition. 12 patients received Clinolipid for a mean of 202 days (range 24-408 days) and 10 patients received the comparator lipid for a mean of 145 days (range 29-394 days). The two groups were not statistically different for weight, weight loss, mid-arm circumference and triceps skinfold thickness. Adverse events and laboratory safety data were comparable for the two lipid groups.

Essential Fatty Acid Status in Adults

Essential fatty acid status in adults was evaluated as a primary objective only in one adult study, C89CSW 6/3 08F (see table in Section 5.2, study duration 15 days to 6 months): Short term studies that last 5-days cannot be considered adequate to monitor EFA status. Fatty acid deficiency on parenteral nutrition may take weeks to develop, especially, when marginal amounts of EFA are being supplied.

The investigators of study C89CSW 6/3 08F consider “a ratio of 20:3n-9/20:4n-6 in excess of 0.4 *suggestive* of EFA deficiency.[14]” Details about this ratio, also known as the Holman index or triene:tetraene ratio, will follow in the safety section. In contrast to the value of 0.2 -0.4 quoted above, the Mayo Medical Laboratories quote the reference range for the triene/tetraene ratios as follows:

[14] Study Report C89CSW 6/3 08F Page 13 of 1596

Age	Triene/Tetraene Ratio
1-31 days:	0.017-0.083
32 days-17 years	0.013-0.050
≥18 years	0.010-0.038
Retrieved from http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82426 on 24/05/2013	

Consequently some authors have adjusted their cutoffs for biochemical EFAD as follows:

Triene/tetraenes ratio	≥ 0.05	mild EFAD
Triene/tetraene ratio	≥ 0.20	severe EFAD [Petrea Cober 2010]

A discussion why this appears appropriate, even using Holman's own approach in setting the 0.2 cut-off, follows in section 7.1.

The results of study C89CSW 6/3 08F (adults) show the following triene/tetraene ratios (Holman index).

Holman Index (a ratio of trienes:tetraenes)	Clinolipid n=18		Intralipid n=19		Test for Difference
	Day 1	End	Day 1	End	
	Mean ± SD		Mean ± SD		
	0.09 (0.09)	0.06 (0.05)	0.11 (0.10)	0.08 (0.09)	Not significant

There are a number of items which are remarkable about these test results from 20 years ago:

1. The means of the indices are outside the normal range of the modern clinical chemistry lab and remain so even after weeks of lipid infusions.
2. The results have a high standard deviation, perhaps reflecting problems with the analytical method
3. Despite the fact that Intralipid contains EFA in abundance, there is no significant decrease (improvement) in the mean Holman index at the end of the study
4. Based on the SD of 0.09 and a mean of 0.08 for the end-of-study Intralipid results 1 or 2 patients of 19 (calculated 1.73 patients) must have had a Holman index above 0.2 or florid EFAD by modern standards. This is surprising because the Intralipid group received EFA in abundance.
5. There are no reference values provided to put these 20-year-old data into context of modern reference ranges.

There are many different hypotheses which could be discussed to explain these counterintuitive results but ultimately this single study does not convince this reviewer that the essential fatty acid status on Clinolipid has been adequately evaluated in adults. New studies are required that have a statistical analysis plan, specify EFA status as primary or secondary outcome, use up-to-date clinical analytical methods and a

prespecified reference range for normal EFA values that can be agreed upon by the nutrition community and FDA.

6.1.1 Methods

While the applicant provided 31 studies and clinical trials only 9 are controlled studies comparing Clinolipid to Intralipid, the listed drug, in adult patients. Of these only three are long-term studies and in one of these only three patients were treated.
The applicant bases their conclusion of 'equivalence' between Clinolipid and Intralipid as far as the provision of calories is concerned on the absence of a significant difference (non-significant p-value) in anthropometric and biochemical parameters[15].
This approach would of course be unacceptable if we did not have substantial other evidence that lipids with comparable fatty acid composition deliver the same amount of useful (i.e., 'metabolizable') energy.

The methods used to support the proposed indication are summarized in the tables "Highlights of study C89 CSW 6/3 08F in adults" and "Highlights of study C89 CSW 6/3 10F in adults". Specific methods that apply to the two adequate and well controlled trials are summarized above in the tables of section 6.1.

6.1.2 Demographics

The applicant has analyzed demographic subsets across studies without identifying a subpopulation where the efficacy in providing adequate calories duffers from the rest of the analysis set. The most important demographic subgroup is pediatric patients. See section 6.1.

6.1.3 Subject Disposition

See section 6.1.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints differ across studies and the review team has taken the approach to evaluate the studies to support the claim that Clinolipid can provide adequate calories as primary endpoint for the purposes of the review. For details, see Sections 6.1 and 5.2 above.

[15] In other words, absence of evidence is taken as evidence of absence. Technically, the studies could be described as "failed superiority trials" which do not establish "equivalence"

6.1.5 Analysis of Secondary Endpoints(s)

The secondary and exploratory endpoints differ across studies and the review team has taken the approach to evaluate the studies according to their ability to provide an adequate amount of fatty acids as secondary endpoint for the purposes of the review. For details, see Sections 6.1 and 5.2 above.

6.1.6 Other Endpoints

See Table in Section 5.2. The applicant asserts that

- ClinOleic maintained better synthesis of longer fatty acid derivatives.
- ClinOleic maintained higher IL-2 levels and lower ESR.
- ClinOleic was associated with improved vitamin E status and lower homocysteine levels[16].

None of these results have been shown to confer a clinical benefit or to improve upon an “adequate supply of lipids for energy and essential fatty acids”

6.1.7 Subpopulations

Pediatrics

The following clinical trials were conducted in the pediatric age group population:

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration
C 88 CSW 6/3 03 F	Evaluate medium-term tolerability and effect on erythrocyte and plasma fatty acid profiles	SC RDO L AC	Clinolipid versus Intralipid 2.5 g/kg/day IV	20 planned 18 treated 8 Clinolipid, 10 Intralipid	2 month-old to 3 year-old patients with acute or chronic surgical or medical conditions	15-120 d

[16] ClinOleic 20% Lipid Injectable Emulsion 2.7.2 Summary of Clinical Pharmacology Studies , page 22 of 24

CT 2402/P14/ 93/F	Evaluate long-term efficacy and safety	SC RD DB AC	Clinolipid versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day) IV	20 planned 18 treated 9 Clinolipid, 9 Intralipid	1 to 18 year-old patients with surgical or medical conditions requiring parenteral nutrition	2 m
CT 2402/P15/ 94/G	Evaluate short-term (7 days) efficacy and safety in premature infants	MC RDD B AC	Clinolipid versus Intralipid escalating: 0.5-2.0 g/kg/day (maximum rate of 6.0 g/kg/day) IV	40 planned 42 treated 22 Clinolipid, 20 Intralipid	Premature newborns requiring total parenteral nutrition	7 d
SC-single center, MC – multi-center, RD – randomized, DB- double blind, OL –open label						

Study C 88 CSW 6/3 03 F had duration of treatment 17 ±5 days and involved 18 patients. The primary and secondary endpoints are not stated. Evaluation of EFA was not stated as a goal. The statistical analysis plan is rudimentary. We are not aware of a sample size calculation.

Study CT 2402/P14/93/F was a randomized, double-blind, single center study conducted from March 1994 to August 1995. Nine patients were randomized and analyzed in each group. The patients ranged in age from 1 – 18 years with an average of 4 years (SD 1.1 years) and 3 years (SD 1.0 years) for the Clinolipid and comparator groups, respectively. The duration of treatment was on average 56 days (range: 53-64 days) in the Clinolipid group and 55 days (range: 36-66 days) in the reference product group. The primary endpoint was the composition of plasma fatty acids; secondary endpoints included nutritional anthropometric measures and albumin levels. The sample size was determined by the availability of patients and was not determined by statistical methods. Evaluation of EFA was not stated as a goal. The lipid dose was individually adjusted.
The increase in plasma and red blood cell C18:1n-9 (oleic acid) and the decrease in C18:2n-6 (linoleic acid) with Clinolipid was consistent with the fatty acid content of the product reflecting its higher oleic acid content compared with the reference product.

While fatty acids were measured, a formal assessment of essential fatty acid status as a declared endpoint was not specified in the analysis plan. Plasma lipid profiles in the two groups were not different except for total cholesterol and LDL-cholesterol which were lower for Clinolipid. Triglycerides were normal in both groups. The two groups were not

statistically different for weight, mid-arm circumference and triceps skinfold thickness. Adverse events and laboratory safety data were comparable for the two lipid groups. As previously stated the design of the study was flawed, however, given the totality of the data, is supportive of an indication of "adequate provision of calories" (see also discussion in section 5.2 Review Strategy).

Study CT 2402/P15/94/G was a randomized, double blind multicenter study conducted from June 1994 to March 1997 in premature infants (28 to 36 weeks). 24 patients were randomized to Clinolipid and 21 to the comparator lipid (22 and 20, respectively, were ultimately treated). The duration of treatment was 7 days. The primary endpoint was the composition of plasma fatty acids (n-6 metabolite fatty acids, n-3 metabolite fatty acids, Mead acid (C20:3n9), and arachidonic acid (C20:4n-6) in plasma. Anthropometric measures were not endpoints in this study but weight was recorded.
No statistically significant differences in the above metabolites were found except for the Mead acid (elevated in EFA) which decreased in the soybean oil based comparator product but remained unchanged in the Clinolipid group (discussed further below).
There were no statistically significant differences in weight between groups before and after start of intravenous lipids. This was expected given the short duration of the study (7 days). Adverse events and laboratory safety data were comparable for the two lipid groups.

Excerpt from a review by the Pediatric and Maternal Health Staff[17]

The Division of Gastroenterology Products consulted the Pediatric and Maternal Health Staff in 2011 to determine whether, as the applicant suggests, the pediatric studies satisfy the requirements of the Pediatric Rule (PREA) is not triggered by this 505(b)(2).

[17] Memorandum.July 13, 2011.Laurie S. Conklin, MD, Medical Officer Pediatric and Maternal Health Staff.

The full document is in the appendix. The following is an excerpt (Comments to the quoted text by this reviewer are in italics):

Comments: It is difficult to apply the typical extrapolation and bridging paradigms to parenteral nutrition. On a very high level the 'disease' could be classified as malnutrition which has numerous underlying causes. In other words, yes, the course of disease is similar, prolonged malnutrition leads to organ dysfunction, failure and death. Exposure response is likewise similar but requires, as in adults, an individualized nutrition prescription.

PMHS believes that the condition of requiring parenteral nutrition "when oral or enteral nutrition is not possible, insufficient, or contraindicated" is similar between adults and children. The Division must feel comfortable that efficacy has been adequately demonstrated in adults before extrapolation could be considered. If extrapolation is used, a rationale must be documented within the review.

Comments: As previously stated this reviewer is satisfied that efficacy in regards to the provision of an adequate amount of calories in adults has been adequately demonstrated and I am also is confident that this can be extrapolated to pediatric patients. However, I am concerned about the adequate provision of essential

fatty acids (which is both an efficacy and safety issue) especially in premature newborns.

• Even when extrapolating efficacy from adults to pediatric patients is appropriate, supportive data is needed fordosing and safety. Since pharmacokinetic data is not available, a study with clinical efficacy endpoints appears to be needed to support dosing and safety, particularly in a growing child. Longer term studies in children are necessary to demonstrate safety in all age groups. It should be demonstrated by the Sponsor that adequate daily doses of ALA and LA will be provided by ClinOleic. Demonstration of adequate essential fatty acid levels is necessary.

Comments: This reviewer agrees with the PMHS assessment and such studies will be recommended as post-marketing requirements and commitments However, the dosing of nutrition products has been standardized in many areas of the world, including the United States. Prescribers of nutrition products follow national or international guidelines and are frequently, at least in the US, subject to auditing by local therapeutics committees. The parenteral nutrition dosing guidelines are based on extensive clinical experience over more than 40 years and have been continuously refined. They have achieved a high degree of maturity and further "dose ranging" studies would appear not only unnecessary but also ethically suspect.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant has not explored new dosing schedules. Dosing of lipid emulsions is individualized by the treating physician based on the individual caloric needs of patients using guidelines published by national and international nutrition societies (see above comments to PMHS consult)

The following dosing guidelines are currently used in different Clinolipid labels approved in other countries/regions. There is some variation because society recommendations have changed, largely towards recommending lower total lipid doses for adults.

Dosing guidelines in labels

	UK/ Europe	**Australia**	**Canada**
Adult	The infusion should be started at a rate of 0.5ml per minute for the first 15-30 minutes. The rate can then be increased to allow 500ml of ClinOleic 20% to be	1 to a **maximum of 2 g** lipids/kg/day. Never exceed 0.15 g lipids/kg/hour (0.75 mL/kg/hour).	The usual dosage is **1 to 2 g** lipids/kg/day. The initial infusion rate must be slow and not exceed 0.1 g lipids or 0.5 mL (10 drops) per minute for 10

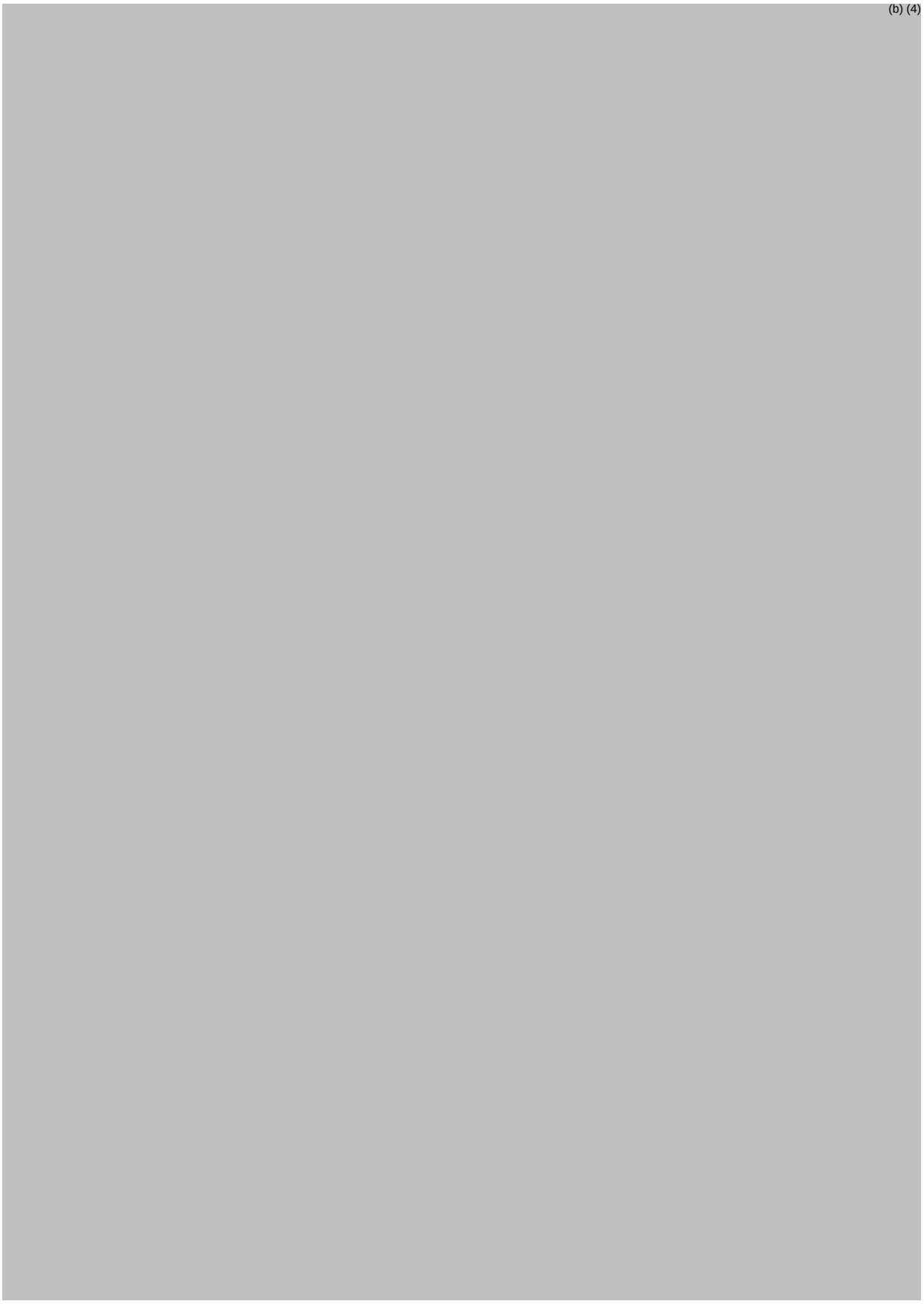
	administered on the first day. On subsequent days the dose may be increased to a **maximum of 2.5g lipids/kg** of body weight with a maximum infusion rate of 0.25 g lipids/kg/hour.		minutes then gradually increased until reaching the required rate after half an hour.
Children	The infusion should be started at a rate of 0.05ml per minute for the first 10-30 minutes. Never exceed an infusion rate of 0.25g lipids/kg/hour. The daily dosage should **not exceed 4g lipids/kg** of body weight.	- recommended not to exceed a daily dose of **3g lipids/kg** of body weight and an infusion rate of 0.15 g lipids/kg of body weight/hour.	None given
Premature infants	In small for gestational age or premature infants with impaired capacity to metabolise fat, initial dosage should be 0.5g lipids/kg/day. This dosage can be increased daily by 0.25g lipids/kg/day up to a **maximum dose of 3g** lipids/kg/day	- restricted to premature infants of 28 weeks gestational age or more. - initial daily dose should be 0.5-1.0g lipids/kg of body weight. - may be increased by 0.5-1.0g lipids/kg of body weight every 24 hours **up to a daily dose of 2.0 g** lipids/kg of body weight.	None given

The dosing guidelines proposed by the applicant for the US label of Clinolipid are acceptable and follow the guidelines issued by ASPEN (American Society for Parenteral and Enteral Nutrition) “Safe Practices for Parenteral Nutrition” closely (J. Mirtallo et al. 2004) . The ASPEN guidelines are widely followed by nutrition practitioners in North America and have a four decades long history of evidence based adjustments and refinements. These guidelines are similar to those of the European sister organization, ESPEN (European Society for Parenteral and Enteral Nutrition).

Our label recommendations for the dosing section are given below.

Label: 2.3 Dosing Considerations

(b) (4)



(b) (4)

Pediatric Patients:

(b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Does not apply. We do not have any data that lipid emulsions have efficacy that persists beyond their metabolic use as source of calories and essential fatty acids. Tolerance, i.e., the need for ever increasing doses to have the same effect, has not been described.

6.1.10 Additional Efficacy Issues/Analyses

Safety and efficacy analysis overlap in the assessment of the adequate delivery of essential fatty acids. A lipid product that cannot supply an adequate amount of fatty acids may both lack efficacy and be considered unsafe in certain circumstances. From a safety perspective an intravenous lipid emulsion for clinical use should be expected to supply adequate amount essential fatty acids to *prevent* the development of fatty acid deficiency. From an efficacy point of view an intravenous lipid product should be able to *restore* essential fatty acids stores when these are low or depleted and keep up with long-term requirements so that essential fatty acid deficiency does not arise while patients are on that product. For further review see section 7.

7 Review of Safety

Safety Summary

1. Mild preexisting essential fatty acid deficiency (EFAD) observed in a 7-day randomized controlled trial involving premature infants, the only trial conducted with premature infants as subjects, was not corrected with Clinolipid but resolved with Intralipid.
2. The adequacy of supply of EFA in the adult, but especially the premature newborn and pediatric patient populations, has not been satisfactorily established.
3. The phytosterol content of Clinolipid and Intralipid are high[18] as is typical for plant derived oils. It has not been established that the phytosterol content of production batches of Clinolipid is lower than those of Intralipid. Phytosterols may be one of the etiologic factors involved in the causation of parenteral nutrition associated liver disease.
4. Clinically relevant benefits of a higher omega-3 FA content and/or a lower omega-6 FA have not been clearly demonstrated in this application or in the literature.
5. Liver test abnormalities are the most commonly observed AE with Clinolipid. In general, Clinolipid is well tolerated.

7.1 Major Safety Issues Identified

This reviewer has identified three safety issues that are of particular relevance: The potential for fatty acid deficiency, possible toxicities related to the phytosterol content of plant derived lipid formulations and the question whether the higher content of omega-3 fatty acids in Clinolipid as opposed to Intralipid confers a safety benefit.

[18] Olive oil has one of the highest phytosterol contents of all plants.

Essential Fatty Acids

Only two specific fatty acids are generally considered to be "essential." They are both long chain (18-carbon) polyunsaturated fatty acids (PUFA) that cannot be synthesized by mammals. Alpha linolenic acid (ALA) is the precursor of the n-3 family of PUFA, in which the first double bond in the molecule is 3 carbons away from the methyl terminus. Linoleic acid (LA) is the precursor of the n-6 PUFA family, in which the first double bond in the molecule is 6 carbons from the methyl terminus.

Mammals lack the requisite enzymes to insert a double bond at the n-3 or n-6 position (counting from the methyl end) of the fatty acid chain (McCowen 2005) .

Docosahexaenoic acid (DHA, 22:6n–3) and arachidonic acid (ARA, 20:4n–6), metabolites of EFA, are important structural components of the highly specialized membranes lipids of the human central nervous system and are therefore particularly important for the neonate. Inadequate provision of EFA in the adult leads to a recognizable EFA deficiency syndrome of which dermatological manifestations are the most prominent. The adult form is easily reversible; in the infant EFA deficiency may have more far-reaching and possibly permanent consequences for neurological development[19] (Uauy et al. 2001), (Innis 2003).

EFA Requirements

The European Food Safety Authority published "Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol" in 2010 and opined that there were not sufficient scientific data to derive an Average Requirement, a Lower Threshold Intake or a Population Reference Intake for the essential fatty acids. Instead, the panel proposed to set an Adequate Intake for linoleic acid (LA) of 4 % of energy requirements, and for alpha-linolenic acid (ALA) of 0.5 % energy requirements based on the lowest estimated mean intakes of the various population groups from a number of European countries, where overt LA and ALA deficiency symptoms are not present (Tetens 2010). The Institute of Medicine using a similar approach but gives their recommendations as total daily intake: 17 g/day for young men and 12 g/day for young women for LA and 1.6 g/day and 1.1 g/day for men and women, respectively, for ALA. *There are no recommendations for newborn or children* (A Report of the Panel on Macronutrients, Subcommittees on Upper Reference Levels of Nutrients and

[19] The supply of essential fatty acids (EFA) affects the structural composition of the brain and myelin sheaths in particular. The functional correlates of these biochemical changes induced by malnutrition include alterations in the waking electroencephalographic activity, visual- and auditory-evoked responses, motor and cognitive development, and social abilities. Sleep-wake cycle organization as well as autonomic nervous system functioning during sleep are perturbed by early human malnutrition. Most of these effects are potentiated by other environmental factors that interact with poor diet in defining the adverse consequences.

Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 2005).

EFA requirements (parenteral nutrition) in premature infants

"In order to prevent biochemical evidence of EFA (essential fatty acids) deficiency, 0.25 g/kg per day linoleic acid should be given to preterm infants. In term infants and older children the supply of 0.1 g/kg per day linoleic acid may be sufficient to prevent EFA deficiency. *When prescribing lipid emulsions the different LA content of the available lipid emulsions needs to be taken into account* " (Koletzko et al. 2005)[20].
The rationale for this recommendation is unclear and not referenced in the document but is described as a Level D recommendation (Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles).

The statement in the European guidelines that "the different *LA content of the available lipid emulsions needs to be taken into account* " is important: For decades only one lipid product has been available in the United States, Intralipid, which supplies EFA in abundance. The potential of EFAD while administering intravenous lipid products which have a lower EFA content, previously not available in the US, has therefore not entered the consciousness of nutrition practitioners in the United States, except in highly specialized newborn intensive care units[21].

Genetic polymorphisms in EFA metabolism

EFA are essential because they are precursors for a number of other higher order derivatives (desaturation and elongation products, LC-PUFAs) (see above and image in Section 2.1). Plasma levels of LC-PUFAs are determined by both dietary intake and endogenous metabolism. Desaturases and elongases catalyze the conversion of PUFAs in humans. The key enzymes in this pathway are the delta-5 and delta-6 desaturases, which are encoded by fatty acid desaturase (FADS) 1 and (FADS) 2 genes, respectively.
An initial candidate gene study reported highly significant associations between FADS gene cluster polymorphisms and fatty acid levels in serum phospholipids with an extraordinary high genetically explained variance for arachidonic acid levels of 28.5%. Carriers of the minor alleles had enhanced levels of desaturase substrates and decreased levels of desaturase products, suggesting a decline in desaturase expression or activity because of the polymorphisms. These results were replicated in several association studies additionally showing an effect in different human tissues as well as in a recent genome-wide association study on LC-PUFA levels (Lattka et al. 2010) .

[20] Referring to intravenous administration (parenteral nutrition)
[21] Personal experience as gastroenterologist, informal survey of colleagues

The clinical relevance of these findings is that there is probably a subset of neonates that have higher requirements for the external provision of EFAs or their metabolites than the average based on genetic polymorphisms that decrease the activity of the desaturases. Recently (2013) the minor allele frequencies were found to range from 21.3% to 30.7% in 409 Danish infants, but in contrast to previous studies, minor allele carriers were identified that were associated with an increased (improved) status of LC-PUFA (Harsløf et al. 2013)

In conclusion, it appears that future studies of the adequacy of provision of EFA to neonates, especially premature infants, by parenteral nutrition should also evaluate polymorphisms of the desaturase (FADS) 1 and (FADS) 2 genes.

Adequacy of analytic methods to determine essential fatty acid status and adequacy of cut-off values for EFAD used by the applicant

As we have seen, national bodies have found it difficult to establish EFA requirements other than establishing values for an "adequate intake". It is not surprising that what exactly constitutes biochemical evidence of an adequate oral intake or a state of deficiency is also not completely clear. Experts agree that this is an issue that has been neglected but needs a broad review[22]. In the past, and this includes the period during which the studies in this NDA were performed, triene/tetraene ratios above 0.2 to 0.4 were considered to be indicative of fatty acid deficiency. The applicant states: "An index >0.2 to 0.4 *suggests* EFAD [italics added][23]" Currently, a level above 0.2 is considered by some evidence of *severe* essential acid deficiency.
The 0.2 to 0.4 level was established by Holman, who did most of the research regarding triene/tetraene ratios, often called the Holman index. Holman used a typical clinical chemistry paradigm starting with normal values for a reference population using standard deviations to arrive at the value outside the normal range: "The triene/tetraene ratio, 20:3ω9/20:4ω6, was found to be 0.1 ± 0.08 for male and female populations, indicating that a ratio above 0.2 should be considered the upper limit of normalcy" (Holman, Smythe, and Johnson 1979).

However, clinical analytical methods have progressed (Lagerstedt et al. 2001) and the Mayo Medical Laboratories quote the reference range for the triene/tetraene ratios much differently as follows:

Age Range	Triene/Tetraene Ratio
1-31 days:	0.017-0.083
32 days-17 years	0.013-0.050
> or =18 years	0.010-0.038
Retrieved from http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82426 on 24/05/2013	

[22] Opinion of academic members of the FDA-ASPEN IVFE Workshop Steering Committee
[23] ClinOleic 20% Lipid Injectable Emulsion Page 122 of 158 2.7.3 Summary of Clinical Efficacy

Values above this reference range should now be considered indicative of essential fatty acid deficiency following the same reasoning Holman applied to his older data. Indeed, recent publications define a triene: tetraene ratio of 0.05 across all age groups as mild EFAD and severe EFAD as a triene: tetraene ratio at least 0.20 (Cober and Teitelbaum 2010).
The discrepancies between the Holman reference range and the current Mayo Laboratories Reference Values can probably be explained by different analytical methods, as Siguel suggests: "The use of old technology, which had inadequate peak separation and erroneous peak integration, led to huge errors in measuring 20:3ω9" (Siguel 1998).

As to the general applicability of the Holman index, Holman himself cautions in 1971:

> The triene:tetraene ratio, although useful as a good rule of thumb, should not be applied arbitrarily … when the chief dietary PUFA is not of the omega-6 family, only the numerator of the ratio is affected and the calculated ratio will not reveal a full picture. The triene:tetraene ratio is valid in most natural dietary situations in which linoleate is the dominant EFA (Holman 1971)

In view of this it appears better to obtain a full panel of fatty acids[24] for clinical trials that aim to evaluate the status of fatty acids and essential fatty acids. Furthermore, the adequacy of data obtained by older liquid chromatography methodologies could be questioned.

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

This study was a prospective, controlled, comparative, randomized, double blind, multicenter study (2 centers) conducted to evaluate the safety and efficacy of ClinOleic ® 20% I.V. Fat Emulsion in premature infants requiring lipid-based total parenteral nutrition for a minimum of 7 days. *The duration of the study was exactly 7 days in all participants.*
Randomization was stratified on birth weight and center. Forty-five patients were enrolled and randomized (Clinolipid: 24, Intralipid: 21). Thirty-three were analyzed for efficacy, 42 for safety. Main inclusion criteria were: Premature infant: gestational age 28 to 36 weeks + 6 days. Needed to be transported to study center within 24 hours after birth. Primary study endpoints: n-6 metabolites fatty acids, n-3 metabolites fatty acids, Mead acid (C20:3n9), Arachidonic acid (C20:4n-6) in plasma

[24] For example: Fatty Acid Profile, Comprehensive (C8-C26), Serum
http://www.mayomedicallaboratories.com/test-catalog/Overview/82042

Secondary: Other fatty acids in plasma, plasma concentration of tocopherols, urinary excretion of malondialdelhyde (MDA).

	Clinolipid n=24	**Clinolipid**	**Intralipid N=21**	**Intralipid**
	Baseline	Day 8	Baseline	Day 8
Holman Index	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: it *deteriorates* slightly in the ClinOleic group (from 0.093 at baseline to 0.112 at day 8) and it *improves* in the Intralipid group (from 0.054 at baseline to 0.020 at day 8).

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

As can be seen, applying more stringent criteria (see above, triene/tetraene ratio of 0.05 indicating mild EFAD), premature infants in both groups were mildly EFA deficient upon entering the study with no improvement, even a slight deterioration numerically, in the Clinolipid group after 7 days and a resolution of the biochemically mild EFAD in the Intralipid group. The question whether subsequent measurements in the infants on Clinolipid would have shown a further increase (worsening) of the Holman index appears both reasonable and concerning. The applicant comments as follows on the results of Study CT 2402/P15/94/G:

> "The data clearly demonstrate the adequacy of essential fatty acid supply using either ClinOleic or the comparator lipid emulsion (Intralipid in 7 studies, IVELIP in 2 studies and LIPOFUNDIN in 1 study), as none of the reported Holman index values approached the threshold values commonly used as indicators of essential fatty acid deficiency (>0.2 to > 0.4). The Holman indices for ClinOleic and for the comparator lipids were comparable in all of the studies, except for Study CT 2402/P15/94/G in pre-term infants (see Table 16). In that study, the mean baseline Holman index for the ClinOleic group was statistically significantly higher than that for the Intralipid group (0.093 vs 0.054, respectively; p=0.03). Mean changes from baseline in the indices increased slightly in the ClinOleic treatment group (to 0.112) and decreased substantially in the Intralipid comparator group (to 0.020). Nonetheless, all of these mean values were well below the published thresholds for EFAD [25]."

[25] ClinOleic 20% Lipid Injectable Emulsion Page 126 of 158 2.7.3 Summary of Clinical Efficacy

The interpretation of the significance of the data by the applicant is based on triene/tetraene reference cut-off values that are much higher than the reference ranges currently used by leading clinical laboratories (see above). This reviewer concludes that the only study in this application that has premature newborns as subjects, the group which is at highest risk of EFAD and most vulnerable to it, raised serious safety concerns regarding the ability of Clinolipid to supply sufficient EFA in this setting.

Essential fatty acid deficiency in adults on intravenous lipid infusions

EFAD in adults on soybean oil-containing lipid formulations has not been described in the literature until 2012 and the applicant states:

> Baxter is not aware of EFAD occurring in patients receiving either ClinOleic or Intralipid as part of their parenteral nutrition regimen (ie, no AEs of EFAD have been reported to Baxter or published in the medical literature). Cases of EFAD that have been reported in the literature result from the administration of lipid-free parenteral nutrition. However, it is clear that an inadequate supply of EFA can lead to EFAD in patients receiving parenteral nutrition[26].

This reviewer has, however, identified a case report where well-documented EFAD developed over 2 weeks in an adult postsurgical patient who received a reduced amount of lipids because of hypertriglyceridemia (Roongpisuthipong et al. 2012) . The product used (Structolipid: soya/coconut/palm kernel oil) has twice the linoleic acid concentration of Clinolipid (Structolipid 33 % weight, Clinolipid 18 % weight, Intralipid 52 % weight). The clinical manifestations of EFAD were fully reversed after the infusion dose was again increased to the recommended target.

This case report raises the concern that certain patients who do not receive the recommended dose of Clinoleic may also be at risk for EFAD, especially in view of the even lower EFA content of Clinolipid compared to Structolipid, a product that is not available in the United States. We requested comments from the applicant in an information request (see following section).

Review of Baxter's Clinical Information amendment 1.11.3

FDA prepared an information request to the applicant with the following questions:

> **FDA's question 1.** You previously stated: "Baxter is not aware of Essential Fatty Acid Disease (EFAD) occurring in patients receiving either ClinOleic or Intralipid as part of their parenteral nutrition regimen (i.e., no Adverse Events (AEs) of EFAD have been reported to Baxter or published in the medical literature). Cases of EFAD that have been reported in the literature result from the administration of lipid-free parenteral nutrition. However, it is clear that an inadequate supply of

[26] 2.7.3 Summary of Clinical Efficacy. ClinOleic 20% Lipid Injectable Emulsion, USP Page 123 of 158

> Essential Fatty Acid (EFA) can lead to EFAD in patients receiving parenteral nutrition."
> FDA has identified a case report where Essential Fatty Acid Disease (EFAD) developed within 2 weeks in an adult postsurgical patient who received a reduced amount of lipids because of hypertriglyceridemia. In particular, we note that the product used appears to have had twice the linoleic acid concentration of Clinolipid.
> This seems to suggest that under certain clinical scenarios, it is possible that EFAD may occur when Clinolipid is the sole source of lipids, especially when the EFA requirements are high (such as in preterm infants) and the daily dose is reduced.
> Please provide your perspective on this case report and provide a list of other clinical scenarios in which patients receiving Clinolipid may be at a higher risk EFAD.

In brief summary, the applicant responded that the case report concerned a patient where multiple factors increased the demand EFA and multiple factors decreased the supply.

However, the applicant conceded that there are clinical scenarios in which patients receiving Clinolipid may be at a higher risk for EFAD (increased demand or at risk due to inadequate supply of EFAs).

- Severely malnourished patients (loss of endogenous fat stores) with high cellular and metabolic demands from disease states or injury (i.e., proliferative malignant diseases, burns, multiple large wounds, refeeding after severe weight loss)
- Patients with hypertriglyceridemia exclusively supported with PN (patients may have a decreased ability to utilize fatty acids)
- Pre-term infants and infants with short bowel syndrome (SBS) with decreased fat stores
- Parenteral nutrition patients with SBS with insignificant oral/enteral nutrient absorption and low parenteral lipid intake
- All patients with lipid intakes below recommended dietary intake levels

> **FDA's Question 2**. We acknowledge your calculation of the Holman index for the 3 submitted pediatric studies; however, we note that:
> a. Study C 88 CSW 6/3 03 F had a treatment duration of 17 ± 5 days and a total of 18 patients. The primary and secondary endpoints are not stated and the evaluation of EFA was not stated as a goal. The statistical analysis plan lacks a sample size calculation.
> b. Study CT 2402/P14/93/F had a mean duration of 56 days. The sample size does appear to have been adequately justified. In addition, evaluation of EFA was not pre-specified as an objective and the lipid dose was individually adjusted at the discretion of the provider.
> c. Study CT 2402/P15/94/G was conducted in premature infants (28 to 36 weeks).The duration of treatment was only 7 days. It does not appear that the

> above studies, by themselves, exclude a risk of EFAD with Clinolipid. We are especially concerned about the absence of adequate long-term data in the population of premature infants. We also note that in the short-term study CT 2402/P15/94/G, the Holman index (group average) associated with Clinolipid was 5 times higher at the end of the 7-day period than the one associated with Intralipid. Although we acknowledge that this was below the cutoff for EFAD[27], this change occurred within 7 days and potentially could have continued to increase if follow-up had been longer. We further note that your data are calculated ratios of reported means. This approach could easily obscure the occurrence of EFA in isolated patients.
>
> Please provide comments on these observations and whether there is existing longer term data that suggests this is not a clinical concern.

In his response the applicant first gives background on the Holman index and summarizes:

> "…very low ratios for the Holman index suggest excess essential fatty acid intake while high levels suggest low intake of essential fatty acids. Triene:tetraene ratios obtained from individuals eating western diets (high in linoleic acid) demonstrate very low values, reflective of the high omega-6 PUFA intake. An understanding of the triene/tetraene ratio is important since a rise in the ratio from very low values may be indicative of a "healthier" lipid intake in which high levels of omega-6 polyunsaturated fatty acids are being reduced. Unfortunately, EFA dose response studies have not been performed in humans to determine the optimal triene:tetraene ratio associated with best health. Despite the lack of data related to dose-response, a triene:tetraene ratio that lies between very low (i.e., <0.05) and high (>0.2-0.4) allows for a balance between endogenous synthesis of fatty acids and exogenous supply of essential fatty acids. It is Baxter's opinion that triene:tetraene ratios of 0.05-0.15 represent balance between adequate essential fatty acid supply and adequate endogenous fatty acid synthesis, while minimizing the risk for excess intake of EFA."

It is noteworthy that Baxter's opinion about the "optimal" triene:tetraene ratio range conflicts with the reference values determined by Mayo (which are widely used in the community[28]).

Triene/Tetraene Ratio	Mayo Reference Lab	Baxter opinion on balanced EFA status
1-31 days:	0.017-0.083	0.05 – 0.15
32 days-17 years	0.013-**0.050**	
> or =18 years	0.010-0.038	
Retrieved from http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82426 on 24/05/2013		

[27] At the time of the request we did not know that some authors have tightened the cut-off value for EFAD from 0.2 – 0.4 to greater than 0.05.
[28] Phone call Dr. Ron Sokol, University of Colorado, 10 June 2013.; Rangel et al. 2012; Dr. Daniel Teitelbaum, personal communication.

If the Mayo clinic upper limit of normal of 0.05 is taken as a cut-off to indicate “mild EFAD” then 7 of 7 patients (100%) in study C88 CSW 6/3 03F (2-57 months of age) on Clinoleic were mildly fatty acid deficient at the conclusion of the study. In contrast, only 4 of 10 patients (40%) on Intralipid had a ratio above 0.05 at Day 15 (conclusion of the study). The applicant points out that 6 of 18 patients (33 %) were essential fatty acid deficient, defined by a triene-tetraene ratio of > 0.4, upon entry into the study.

Based on a reinterpretation of the data in the light of modern reference values it appears that Intralipid was much more successful in completely reversing the EFAD while Clinolipid improved it but not into the reference range established by the Mayo lab with all children on Clinolipid still being mildly fatty acid deficient.
However, if the applicant proposed ”optimal” triene:tetraenes ratio range were to be used , every child would have been in the “optimal’’ range. Baxter has no data, literature or expert opinion to support their proposed “optimal” range.

Suboptimal delivery of EFA to children already EFA deficient in this age range (2-57 month) could have long-term consequences for their neurodevelopment
Even more concerning are the data for the premature newborns briefly mentioned above and discussed more fully in the safety section. The applicant simply confirms that they have no data extending beyond the 7 day study period in this patient population.

Phytosterols

Phytosterols are plant sterols that are poorly absorbed by the gut and compete with the absorption of cholesterol. Increased oral phytosterol consumption can lower plasma cholesterol levels. However, phytosterols are also contained in intravenous lipid formulations. In contrast to the intestinal route, where the absorption is approximately 5 %, all of the phytosterols contained in intravenous lipid formulations reach the liver. Phytosterols have been implicated as one of several potential causative factors of parenteral nutrition associated liver disease. 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). The applicant of this NDA concedes that “the phytosterol content of the lipid emulsions provided as part of PN therapy is one factor associated with the development of PNALD. Current evidence does not support phytosterol intake as the specific etiologic agent for development of PNALD; however, clinical/research evidence suggests that markedly increased levels of phytosterols contribute to development of PNALD in susceptible patients (i.e., patients with multiple risk factors)[29]”

[29] ClinOleic 20% Lipid Injectable Emulsion, Review of PNALD Publications Page 57 of 67

The applicant continues that “both the phytosterol content and the omega-6 polyunsaturated fatty acid content of lipid emulsions are risk factors for development of PNALD” and that “ClinOleic has the lowest phytosterol content of all plant-based emulsions”. Baxter believes that providing a lipid emulsion product with a lower phytosterol content than current US-approved soybean oil-based lipid emulsions offers a major improvement in PN for all patients, including high-risk populations.”

There are currently no clinical studies that have isolated the two lipid product related purported etiologic factors for PNALD: the content of omega-6 FA and the content of phytosterols. For example, fish oils have a very low in omega-6 FA and, at the same time, do not contain phytosterols. While there is now some evidence that fish oil may have benefits in the treatment of PNALD (Tillman 2013) it is not clear whether this would be due to the absence of phytosterols , their decreased omega-6 content, or a combination of factors.

We will examine the “belief” that the lower omega-6 content confers a safety benefit further on but will first turn our attention to the claim that the phytosterol content of Clinolipid is lower than that of the RLD, Clinolipid.

Phytosterol content of Clinolipid

The applicant presents a table of phytosterol content based on three studies [30].

Table 3.
Content of Phytosterols in ClinOleic and Intralipid

	Intralipid	**ClinOleic**
Manufacturer	(b) (4)	Baxter Healthcare Corporation
Lipid components	soybean oil	olive oil/ soybean oil
Phytosterol Concentration (µg/mL)		
Publication: Xu et al, 2012[I]		
Copyright Material Withheld		

[30] ClinOleic 20% Lipid Injectable Emulsion, Review of PNALD Publications Page 55 of 67

Publication: Forchielli et al, 2010
Copyright Material Withheld
Publication: Ellegard et al, 2005
Copyright Material Withheld

[a] P <0.05 compared to Intralipid.

[b] Compared to Intralipid

[c] Values converted from mg/kg fat values reported in publication: mg/kg fat = mg/5 L (based on 20% emulsion) = µg/mL.

Source: Refer to Xu, 2012,; Forchielli, 2010,[; and Ellegard 2005, .

While these data seem to show that the phytosterol content of Clinolipid is lower than that of Intralipid, the A.S.P.E.N. Position Paper: Clinical Role for Alternative Intravenous Fat Emulsions quotes approximately the same phytosterol content for Intralipid (348 ± 33 mg/L) and Clinolipid (327 ± 8 mg/L)[31] (Vanek et al. 2012) .

Baxter, the manufacturer of Clinolipid, currently does not determine phytosterol levels in their production lots and has no validated analytical method to do so (Teleconference May 20, 2013) but has since proposed an analysis plan that is acceptable to the CMC reviewers.

Phytosterol contents of lipid emulsions depend on the sources of olive and soybean oil, the season, production methods, the age of the product and analytical methods (determination of free or free and esterified phytosterols), amongst other factors (Phillips et al. 2002). Given the uncertainties of the pathophysiological role of phytosterols and squalene[32], no safe limits have been determined by any standard setting body.
In summary, while there may be differences in the absolute concentrations of phytosterols between different products and different batches or lots, it can be said that both soybean oil and olive oil contain substantial amounts of phytosterols and that phytosterols may be an etiologic factor in PNALD.

[31] This reviewer was not able to trace the source of the data presented in the position paper. However, according to personal conversations with outside experts, olive oil tends to have lower phytosterol content in general.
[32] Squalene is a 30-carbon straight-chain hydrocarbon steroid precursor produced by both plant and animal cells. In plants, squalene is cyclized to form phytosterols in animals to form cholesterol.

Does the higher content of omega-3 fatty acids in Clinolipid as opposed to Intralipid confer a safety benefit?

Beliefs that a lower content of omega-6 [33](associated with a higher content of omega-3) may reduce the incidence of PNALD are not substantiated by the data submitted in this NDA or by the literature. None of the studies in this NDA were designed to investigate the issue and the applicant does not attempt to include any related claims in the label. A recent systematic review conducted by the American Pediatric Surgical Association Outcomes and Clinical Trials Committee concludes: "There are insufficient data to recommend the use of SMOF or other hybrid lipids in the treatment of PNAC" (Rangel et al. 2012) PNAC: Parenteral Nutrition Associated Cholestasis. SMOF: combination of soybean, medium-chain triglycerides, olive oil, and fish oil lipid emulsions.

However, there is also a strong bias in favor of lipid emulsions with lower omega-6 content such as Clinolipid for other reasons, for example, expressed in a position paper by ASPEN, and also in a letter to the Director for the Center of Drug Evaluation and Research, Dr. Janet Woodcock[34]:

> "Based on substantial biochemical and clinical evidence, alternative oil-based IVFEs may have less proinflammatory effects, less immune suppression, and more antioxidant effects than the standard SO IVFEs and may potentially be a better alternative energy source. However, the evidence for the clinical use of these alternative IVFEs is still not clearly defined, particularly with regard to specific indications, because of the heterogeneity in the published studies in the patient populations studied, the differences in IVFEs studied, the wide variations in biochemical markers studied, and the lack of consistent clinical outcome data (Vanek et al. 2012)"

The applicant suggests the following language in the proposed label (14. Clinical Studies):

(b) (4)

[redacted]

[33] By itself, i.e., not associated with other changes, such as lower total dose ("lipid reduction") or lower phytosterol content (because of lower dose).
[34] Letter dated December 27, 2012 entitled "Urgent need for making newer alternative intravenous fat emulsions (IVFE) available in the United States (U.S.)" : "Based on substantial biochemical and clinical evidence, the newer, alternative IVFEs have: 1. Less pro-inflammatory effects 2. Less immune suppression 3. More antioxidant effects 4. Act as a better alternative energy source than standard SO IVFE for many critically-ill patients 5. Lower the risk of parenteral nutrition-associated liver disease (PNALD)"

This language appears to be intended to support the bias currently existing in the nutrition community. However, neither are the results of inflammatory or oxidative markers consistent nor have they been associated with any clinical benefit.
Instead of the language proposed by the applicant FDA should include labeling that puts potential implied claims into their current scientific context.

Other safety issues

Other major safety issues involving lipid injectable emulsions include impairments in plasma clearance in susceptible patients related to the infusion of an unstable emulsion containing large quantities of potentially embolic fat globules [Driscoll 2006]. These issues, as well as others, such us stability, trace element and aluminum content, etc., are within the purview of CMC review.

7.2 Methods

7.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data in human subjects were provided from the following sources:

- Integrated safety data from Baxter-sponsored studies of ClinOleic and 3-chamber parenteral nutrition formulations containing ClinOleic (i.e., OLICLINOMEL, OLIMEL, and NUMETA);
- 37 Periodic Safety Update Reports for ClinOleic, OLICLINOMEL, OLIMEL, and NUMETA (from November 1995 to May 2012);
- A supplemental safety analysis of data from Study BE 1000586 (a 2-part retrospective chart review comparing parenteral nutrition in patients who received ClinOleic or soybean oil-based lipid emulsions in Germany); and
- A review of published literature on ClinOleic.

The applicant grouped the 23 Baxter-sponsored studied into ten analysis sets: seven sets included data from the studies performed in adult patients, and three sets include data from the studies in pediatric patients. The applicant performed the primary analyses using the set of comparative studies in which Intralipid was used as the comparator. The analyses performed with the other nine sets of studies were considered secondary analyses.

The analysis sets were based on the patient age category (adult or pediatric), study control (comparative or single-arm), lipid comparator (Intralipid only or all comparator lipids), and duration of study lipid treatment (short-term [planned duration 7 days or less] or long-term [planned duration more than 7 days]).

It is this reviewer's opinion that a comparison of incidence rates of AEs between Clinolipid and Intralipid across pooled disparate studies has little if any meaning and these tabulations will not be reproduced in this review.

7.2.2 Categorization of Adverse Events

Clinical safety outcomes were evaluated by the incidence of adverse events (AEs) categorized by MedDRA system organ class (SOC) and preferred term and other clinical outcomes, depending on the study. In the ClinOleic studies, many safety assessments were also considered biomarkers of nutritional efficacy. These consisted of anthropometric indices (body weight, body mass index (BMI), mid-arm circumference, triceps skin fold, cranial circumference); measurements of protein metabolism. (prealbumin, albumin, transferrin, total proteins, gamma globulins, protein catabolic rates, nitrogen excretion in the urine, nitrogen balance, 3-methylhistidine excretion); and measurements of lipid metabolism (triglycerides, cholesterol (total, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein), phospholipids, apolipoprotein levels, fatty acid levels (including triglyceride, phospholipid, cholesterol ester, cellular fractions)

For laboratory safety assessments see section 7.3.4.

7.2.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For the safety analysis in adults the applicant pooled and analyzed studies as follows: 9 Comparative Studies vs. Intralipid, 14 Comparative Studies vs. All Lipids, 7 Short-term Comparative Studies , 7 Long-term Comparative Studies, 4 Single arm Studies, 19 Comparative and Single arm Studies, 11 Short-term Comparative and Single arm Studies.

For the safety analysis in pediatric patients the applicant pooled and analyzed the following studies: 3 Comparative Studies vs Intralipid, 1 Single-arm Study, 4 Combined Comparative and Single-arm Studies.

The applicant performed exploratory exposure-adjusted analyses for the comparative studies versus Intralipid which appears reasonable to this reviewer based on the disparities of the time period of exposure between studies.

7.3 Adequacy of Safety Assessments

7.3.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In comparative studies, patients received ClinOleic or a soybean oil-based lipid; in single-arm studies they received ClinOleic only. A total of 871 patients (adult, 634; pediatric, 237) were treated in the 23 studies. Of these, 584 patients (adult, 386; pediatric, 198) received ClinOleic, and 287 (adult, 248; pediatric, 39) patients received a soybean oil-based lipid. Dosing was individualized to the needs of individual patients (see below).

7.3.2 Explorations for Dose Response

Explorations for dose response are not applicable to this submission because the doses of lipid emulsions were determined according to the needs of the patient (mostly based on calorie requirements) which were in turn determined according to clinical practice and society recommendations prevailing when these studies were conducted, mostly in the 1990s. Societies have made minor adjustments in their dosing recommendations since that time and these changes are fully reflected in the dosing recommendations Baxter has in their proposed label. The parenteral nutrition dosing guidelines are based on extensive clinical experience over more than 40 years and have been continuously refined. They have achieved a high degree of maturity and further “dose ranging” studies would appear not only unnecessary but also ethically suspect.

7.3.3 Special Animal and/or In Vitro Testing

Studies performed in the mouse, rat, rabbit, and dog support the safety of ClinOleic inhuman subjects.

7.3.4 Routine Clinical Testing

Laboratory safety evaluations comprised assessments of hematologic function (hemoglobin, hematocrit, leukocytes, platelets, differential counts [neutrophils, lymphocytes, monocytes, basophils, eosinophils]); hemostasis (prothrombin time, activated partial thromboplastin time, activated clotting time, fibrinogen, clotting factors); hepatobiliary function (aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma glutamyl transferase, bilirubin (total and conjugated), bile acids, sometimes lactic dehydrogenase, ultrasound); renal function (blood urea nitrogen, creatinine); endocrine function (glucose, insulin); electrolyte function (Na, K, Cl, CO2, Ca, PO4, Mg); and acid-base status (blood gas [PO2, PCO2, pH, HCO3, base excess]).

7.3.5 Metabolic, Clearance, and Interaction Workup

ClinOleic lipid emulsion (b) (4), and its distribution and metabolism are similar to that of endogenously synthesized chylomicrons. ClinOleic is administered into the venous system (peripheral or central vein) and distributes systemically; there is no first pass hepatic metabolism. After administration, the circulation of ClinOleic is similar to that of endogenous chylomicrons, which originate in the GI tract following absorption and enter the systemic venous system (brachiocephalic vein) via the thoracic duct. Subsequent metabolism occurs though triglyceride hydrolysis (via lipases) to glycerol and free fatty acids. Since ClinOleic and Intralipid, the RLD, have a similar globule size distribution, both are metabolized via the same enzymatic pathways. The applicant evaluated appropriate clinical chemistry parameters such as triglyceride clearance and no significant differences were found,

7.3.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See section 7.2.3. The applicant analyzed 9 comparative studies Clinolipid vs. Intralipid.

7.4 Major Safety Results

7.4.1 Deaths

The following table describes all 18 deaths that occurred in 19 Combined Comparative and Single-arm Studies in patients who received Clinolipid [35]. There were no deaths in the pediatric studies.

Applicant's Table 91. Fatal Serious Adverse Events Reported for ≥ 1 Adult Patient
(19 Combined Comparative and Single-arm Studies)

MedDRA Preferred Term[b]	Number (%) of Patients[a]
	ClinOleic (N=386)[c, d]
Septic shock	5 (1.3)
Subarachnoid haemorrhage	2 (0.5)
Cardiac arrest	1 (0.3)

[35] ClinOleic 20% Lipid Injectable Emulsion Page 194 of 828 Integrated Summary of Safety

Cerebral infarction	1 (0.3)
Death	1 (0.3)
Gastric cancer	1 (0.3)
General physical health deterioration	1 (0.3)
Haemodynamic instability	1 (0.3)
Hepatorenal failure	1 (0.3)
Mediastinitis	1 (0.3)
Peritoneal haemorrhage	1 (0.3)
Pneumonia	1 (0.3)
Pneumothorax	1 (0.3)

[a] Patients with multiple AEs at the same severity grade were counted only once for a specific AE.

[b] MedDRA version 13.0.

[c] Only ClinOleic data are analyzed when comparative and single-arm studies are combined.

[d] Descending order of frequency, "ClinOleic" column.

MedDRA = Medical Dictionary for Regulatory Activities.

It is this reviewer's opinion that none of these deaths are directly attributable to Clinolipid.

In comparative studies Clinolipid vs. Intralipid 6 out of 192 subjects in the Clinolipid group died vs. 3 of 179 in the Intralipid group. This reviewer has no reason to believe that this numerical imbalance is not due to chance.

Fatal Serious Adverse Events in Adult Patients (9 Comparative Studies vs. Intralipid)

MedDRA Preferred Term[b]	Number of Patientsa	
	ClinOleic[c] (N=192)	Intralipid (N=179)
Subarachnoid haemorrhage	2	0
Hepatorenal failure	1	0
Mediastinitis	1	0
Peritoneal haemorrhage	1	0
Pneumothorax	1	0
Encephalitis	0	1
Intestinal infarction	0	1
Renal failure	0	1

Adapted from applicant's Table # 50 ClinOleic 20% Lipid Injectable Emulsion
Page 108 of 125 2.7.4 Summary of Clinical Safety

7.4.2 Nonfatal Serious Adverse Events

The following table shows SAEs between Clinoleic and Intralipid. There are no specific safety signals for Clinolipid [36].

Applicant's Table A5.5.1. Summary of SAE Incidence
Adult comparative studies with Intralipid as comparator

System Organ Class Preferred Term	ClinOleic (N=192) n (%)	Intralipid (N=179) n (%)
Any Serious Adverse Event	9 (4.7)	5 (2.8)
INFECTIONS AND INFESTATIONS	4 (2.1)	3 (1.7)
SEPSIS	2 (1.0)	1 (0.6)
MEDIASTINITIS	1 (0.5)	0 (0.0)
STAPHYLOCOCCAL SEPSIS	1 (0.5)	2 (1.1)
NERVOUS SYSTEM DISORDERS	2 (1.0)	1 (0.6)
SUBARACHNOID HAEMORRHAGE	2 (1.0)	0 (0.0)
ENCEPHALITIS	0 (0.0)	1 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.5)	0 (0.0)
PNEUMOTHORAX	1 (0.5)	0 (0.0)
GASTROINTESTINAL DISORDERS	1 (0.5)	1 (0.6)
PERITONEAL HAEMORRHAGE	1 (0.5)	0 (0.0)
INTESTINAL INFARCTION	0 (0.0)	1 (0.6)
HEPATOBILIARY DISORDERS	1 (0.5)	0 (0.0)
HEPATORENAL FAILURE	1 (0.5)	0 (0.0)
RENAL AND URINARY DISORDERS	0 (0.0)	1 (0.6)
RENAL FAILURE	0 (0.0)	1 (0.6)

All percentages are based on the number of safety subjects in the treatment group.
A subject is only counted once for multiple events within a MedDRA classification.

[36] ClinOleic 20% Lipid Injectable Emulsion Integrated Summary of Safety Page 561 and 562 of 828

7.4.3 Dropouts and/or Discontinuations

In the comparative studies versus Intralipid, 90% of patients in either treatment group completed the study in which they had enrolled (3 patients, 2 ClinOleic and 1 Intralipid, did not have disposition data and were not included in the analysis).
In the other six adult analysis sets, the completion rate was high (≥ 85%). Deaths occurred infrequently and in ClinOleic-treated patients only (<2%). Discontinuations due to AEs, physician decision, protocol violation, lost-to-follow-ups, and withdrawal by patient were infrequent (generally in <2% of patients for each of the preceding categories, except AEs, where the highest rate was 6.1% in the soybean oil-based comparator lipid arm of the long-term comparative studies vs. all lipids).

7.4.4 Significant Adverse Events

The applicants table given below[37] shows adverse events for Clinolipid ordered in descending order by frequency and arranged by categories related, not related and not known. The term 'cell death' refers to the following ontology: General disorders and administration site conditions - Tissue disorders NEC - Necrosis NEC - cell death and refers in all likelihood to infusion site extravasation and Injection site irritation.
The terms blood alkaline phosphatase increased, cholestasis, gamma-glutamyltransferase increased, and hepatic function abnormal could be collapsed under "Hepatobiliary Disorders". If done, it would be the most common adverse event with 33 overall AEs of which 10 were determined as treatment related and 9 unknown whether related or not.

Applicant's Table 51. Adverse Events Reported for ≥ 3 Adult ClinOleic-Treated Patients by Treatment Relationship (19 Combined Comparative and Single-arm Studies)

MedDRA Preferred Term[c]	Number (%) of Patients[a]			
	ClinOleic[b] (N=386)			
	Overall Incidence[d]	Related[38]	Not Related	Unknown
Hepatic enzyme increased	*19 (4.9)*	4 (1.0)	7 (1.8)	8 (2.1)
Nausea	*16 (4.1)*	8 (2.1)	8 (2.1)	0
Vomiting	*13 (3.4)*	4 (1.0)	9 (2.3)	0
Anaemia	*12 (3.1)*	0	12 (3.1)	0
Hyperglycaemia	*11 (2.8)*	10 (2.6)	1 (0.3)	0
Pyrexia	*8 (2.1)*	2 (0.5)	6 (1.6)	0
Neutrophil count increased	*8 (2.1)*	0	5 (1.3)	3 (0.8)

[37] ClinOleic 20% Lipid Injectable Emulsion Integrated Summary of Safety Page 130 of 828
[38] As determined by the principal investigator

Hypoproteinaemia	*7 (1.8)*	1 (0.3)	6 (1.6)	0
Tachycardia	*7 (1.8)*	2 (0.5)	5 (1.3)	0
Diarrhoea	*7 (1.8)*	2 (0.5)	5 (1.3)	0
Gallbladder disorder	*7 (1.8)*	1 (0.3)	0	6 (1.6)
Gamma-glutamyltransferase increased	*7 (1.8)*	2 (0.5)	4 (1.0)	1 (0.3)
Cough	*6 (1.6)*	0	6 (1.6)	0
Abdominal pain	*6 (1.6)*	2 (0.5)	4 (1.0)	0
Muscle spasms	*6 (1.6)*	6 (1.6)	0	0
Blood triglycerides increased	*6 (1.6)*	4 (1.0)	2 (0.5)	0
Sepsis	*5 (1.3)*	0	2 (0.5)	3 (0.8)
Septic shock	*5 (1.3)*	0	3 (0.8)	2 (0.5)
Infusion site swelling	*5 (1.3)*	0	5 (1.3)	0
Cell death	*4 (1.0)*	4 (1.0)	0	0
Hypokalaemia	*4 (1.0)*	0	4 (1.0)	0
Insomnia	*4 (1.0)*	0	4 (1.0)	0
Hypertension	*4 (1.0)*	1 (0.3)	3 (0.8)	0
Hypotension	*4 (1.0)*	1 (0.3)	3 (0.8)	0
Abdominal distension	*4 (1.0)*	1 (0.3)	3 (0.8)	0
Constipation	*4 (1.0)*	0	4 (1.0)	0
Hyperthermia	*4 (1.0)*	1 (0.3)	3 (0.8)	0
Infusion site extravasation	*4 (1.0)*	0	4 (1.0)	0
Blood alkaline phosphatase increased	*4 (1.0)*	3 (0.8)	1 (0.3)	0
Lymphangitis	*3 (0.8)*	3 (0.8)	0	0
Headache	*3 (0.8)*	1 (0.3)	2 (0.5)	0
Productive cough	*3 (0.8)*	0	3 (0.8)	0
Respiratory failure	*3 (0.8)*	1 (0.3)	2 (0.5)	0
Rhinorrhoea	*3 (0.8)*	0	3 (0.8)	0
Cholestasis	*3 (0.8)*	1 (0.3)	2 (0.5)	0
Hepatic function abnormal	*3 (0.8)*	1 (0.3)	2 (0.5)	0
Asthenia	*3 (0.8)*	1 (0.3)	2 (0.5)	0
Injection site irritation	*3 (0.8)*	3 (0.8)	0	0
Medical device complication	*3 (0.8)*	1 (0.3)	0	2 (0.5)
Blood pressure decreased	*3 (0.8)*	3 (0.8)	0	0
Urine output decreased	*3 (0.8)*	0	3 (0.8)	0

[a] Patients with multiple AEs at the same severity grade were counted only once for a specific AE.

[b] Only ClinOleic data are analyzed when comparative and single-arm studies are combined.

[c] MedDRA version 13.0.

[d] Descending order of frequency, ClinOleic "Overall Incidence" column AE=adverse event;

MedDRA = Medical Dictionary for Regulatory Activities.

7.4.5 Submission Specific Primary Safety Concerns

See section 7.1. This reviewer has identified three safety issues relevant to the class of products, intravenous lipid emulsion, that are of particular relevance: The potential for essential fatty acid deficiency, possible toxicities related to the phytosterol content of plant derived lipid formulations and the question whether the higher content of omega-3 fatty acids in Clinolipid as opposed to Intralipid confers a safety benefit.

7.5 Supportive Safety Results

7.5.1 Common Adverse Events

See section 7.4.4

7.5.2 Laboratory Findings

In the comparative studies versus Intralipid, there were no clinically meaningful differences between ClinOleic- and Intralipid-treated patients for mean changes from baseline to end-of-treatment values in clinical hematology and chemistry laboratory values. This observation was also true for randomized patients in the comparative studies versus all lipids, short-term comparative studies versus all lipids, and long-term comparative studies versus all lipids.
There were also no clinically meaningful differences for changes in these laboratory values from baseline to end-of-treatment for ClinOleic-treated patients in the single-arm studies, combined comparative and single-arm studies, and combined short-term comparative and single-arm studies.

7.5.3 Vital Signs

In the comparative studies versus Intralipid, there were no clinically meaningful differences between ClinOleic- and Intralipid-treated patients for changes in vital signs weight, and BMI from baseline to end-of-treatment. This observation was also true for the comparative studies versus all lipids, short-term comparative studies, and long-term comparative studies. There were also no clinically meaningful differences in changes in vital signs, weight, and BMI from baseline to end-of-treatment for ClinOleic-treated patients in the single arm studies; comparative and single-arm studies; and short-term comparative and single arm studies.

7.5.4 Electrocardiograms (ECGs)

Not applicable.

7.5.5 Special Safety Studies/Clinical Trials

The applicant provided a "Review of Publications on Parenteral Nutrition associated Liver Disease and the Role of Phytosterols", and a discussion of the "Adequacy of Essential Fatty Acid Delivery" in the Summary of Clinical Efficacy. These were referenced in Section 7.1.

7.5.6 Immunogenicity and Immunology Considerations[39]

Lipid emulsions have a very low potential to elicit an immunological reaction so because naturally occurring fatty acids do not elicit an immune response. However, allergic reactions to excipients and impurities are possible. Chief of these would be soy protein allergies. These are rare and in fact soy milk is almost always tolerated by children with a cow milk allergy (Cordle 2004). Documented allergies related to soy protein components in lipid emulsions are even rarer (Gura et al. 2005) .

In contrast, as previously mentioned, there is a bias that Clinolipid (and similar products) may lead to less immune suppression than lipid formulations with higher omega-6 PUFA content, such as Intralipid. See footnote [26].

In an information request to Baxter FDA asked for a review of all studies that compared biochemical and clinical parameters relevant to immune function between Clinolipid and soybean oil-based products.

The applicant concludes[40]:

> "Immune/inflammatory reactions were assessed in a variety of studies using a large number of different tests that included CRP (9 studies), ESR (2 studies), IL-6 (6 studies), TNF (6 studies), IL-2 (1 study), sRIL-2 (1 study), IL-1ra (2 studies), IL-8 (1 study), IL-10 (3 studies), gammaglobulins (2 studies), PGE2 and PGF2α (1 study), HLA-DR (1 study), and granulocyte/monocyte phagocytosis and oxidant burst (2 studies). The studies assessed both secretory (i.e. cytokine) and cellular responses. The results are consistent across studies and demonstrate the lack of significant differences in responses in patients receiving Clinolipid or a soybean oil based lipid emulsion.

[39] This subparagraph was intended by the template designers to discuss the possibility of an immune response elicited by a drug or biological but we will extend the discussion to nutritional immunology.
[40] Baxter. 1.11.3 Clinical information amendment. ClinOleic 20% Lipid Injectable Emulsion

> Overall, the data from a number of clinical studies indicate that Clinolipid and soybean oil based lipid emulsions produce similar effects upon the immune/inflammatory and oxidative systems during infusion as part of parenteral nutrition in a large variety of pathological states. In a small number of studies, Clinolipid resulted in lower inflammatory and/or oxidative responses."

This is an assessment which is at variance with the published ASPEN opinion (see above (Vanek et al. 2012)): "Based on substantial biochemical and clinical evidence, alternative oil-based IVFEs may have less proinflammatory effects, less immune suppression, and more antioxidant effects than the standard SO IVFEs and may potentially be a better alternative energy source." It appears therefore necessary to address this absence of a benefit of Clinolipid over Intralipid in the label, for example, by stating:

> A lower content of omega-6 fatty acids in Clinolipid compared to the listed drug, Intralipid, has not been shown to be associated with beneficial effects upon the immune/inflammatory and oxidative systems and no improved clinical outcomes have been demonstrated.

7.6 Other Safety Explorations

7.6.1 Dose Dependency for Adverse Events

Explorations for dose response are not applicable to this submission because the doses of lipid emulsions were determined according to the needs of the patient (mostly based on calorie requirements) which were in turn determined according to clinical practice and society recommendations prevailing when these studies were conducted.

7.6.2 Time Dependency for Adverse Events

Given the underlying comorbidities of the studied patient populations, adverse reactions were more commonly seen with longer treatment durations. However, there appears to be no causal effect of Clinolipid on the incidence of adverse events over time. In two adult analysis sets, the comparative studies versus Intralipid and comparative studies versus all lipids, the ClinOleic groups had higher number of patients and longer durations of treatment than the comparator groups. These circumstances resulted in an approximately 36% increase in the respective number of therapeutic days (3782 vs 2775 days of lipid exposure) in the former set and an approximately 20% increase in the respective number of therapeutic days (5638 vs 4693 days of lipid exposure) in the latter set: these differences in exposure could account for the slightly higher overall incidence of AEs in the respective ClinOleic groups. The exposure summary by different trial groups is in the appendix.

To account for these differences, exploratory analyses were performed for the comparative studies versus Intralipid and the comparative studies versus all lipids. The exploratory exposure-adjusted analyses for the comparative studies versus Intralipid indicated that the numbers of patients with AEs and overall numbers of AEs are similar between treatment groups.

7.6.3 Drug-Demographic Interactions

Adverse events were analyzed by gender. Clinolipid was well tolerated in men and women. Adverse events were analyzed by medical history/concomitant illness: patients with injury or surgery requiring ICU stay; medical/surgical patients; gastrointestinal surgery patients; burn patients requiring ICU stay; hemodialysis patients; and patients with intestinal failure receiving parenteral nutrition at home. Clinolipid was well tolerated in these special groups of patients. ClinOleic was well tolerated in adult patients who received treatment for up to 438 days and pediatric patients who received treatment for up to 63 days.

Adverse events were analyzed by age category (<65 and ≥ 65 years of age and <75 and ≥75 years of age. ClinOleic was well tolerated in patients in the respective age categories, and no specific safety concerns were identified.

Analyses of safety data for pediatric patients were performed for all AEs); SAEs, including fatal SAEs; fatal SAEs, clinical laboratory evaluations; and vital signs. ClinOleic was well tolerated in pediatric patients. While the applicant has not identified any specific safety concerns for the pediatric population, this reviewer is concerned about the adequacy of provision of EFAs, particularly in preterm infants; see section 7.1.

7.6.4 Drug-Disease Interactions

Not explored.

7.6.5 Drug-Drug Interactions

Not explored and not applicable.

7.7 Additional Safety Evaluations

7.7.1 Human Carcinogenicity

Not explored. No chronic toxicity, genotoxicity, carcinogenicity studies, or fetal toxicity/developmental studies were conducted in animals, as they were not considered appropriate for a nutritional product intended for IV administration.

7.7.2 Human Reproduction and Pregnancy Data

No studies of ClinOleic have been performed in pregnant or lactating women.

7.7.3 Pediatrics and Assessment of Effects on Growth

See concern about inadequate provision of EFA in the premature infant which could affect neurological development adversely; section 7.1.

7.7.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.8 Additional Submissions / Safety Issues

See section 7.1.

8 Postmarket Experience

Adult studies

The applicant submitted 17 papers published between 1992 and 2010, including a total of 291 patients. 13 were comparative studies between patients who received ClinOleic versus some other lipid emulsion (soy, SMOF, MCT/LCT structured lipids). Endpoints were different among studies and included: BMI, albumin, hematology, septic episodes, mortality, hospital length of stay, ICU length of stay, liver function tests, mean heart rate, central venous pressure, catheter infections, other infections, unplanned admissions, thrombotic episodes, adverse events, hemofilter longevity, organ failure, duration of ventilation, respiratory quotient, and inflammatory markers. Eight studies evaluated metabolic effects, including serum triglycerides, cholesterol, and glucose. Overall, Baxter states that all 17 studies demonstrated “no significant differences in clinical outcome, safety, or serum inflammatory marker levels between patients who received ClinOleic and those who received MCT/LCT, or structured lipid emulsions.

Pediatric studies

A total of 10 pediatric literature- based studies (1996 through 2009) have been submitted by Baxter. All were comparative studies between patients receiving ClinOleic vs. another lipid formulation (soy or MCT/LCT). These studies evaluated a total of 322 patients. Exposure time ranged from 5 to 56 days. Patients exposed ranged from preterm infants <37 weeks gestational age to 18 years of age. Like in the adult studies, outcomes are variable, including anthropomorphic parameters, liver function tests, BUN, electrolytes, total and conjugated bilirubin, bile acids, coagulation studies, necrotizing enterocolitis, incidence of bronchopulmonary dysplasia, and intraventricular hemorrhage.

Seven studies reported inflammatory markers as a study outcome. Eight studies reported metabolic effects, such as levels of alpha-tocopherol, HDL levels, LDL levels, and vitamin E status. Baxter again concludes from these studies that there were no

significant clinical outcome or safety differences between ClinOleic and soybean oil-based lipid emulsions in pediatric populations.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The following labeling recommendations are based on the case that Clinolipid is approved for adult (b) (4) populations but the label can be easily modified if the final decision is for an approval in the adult population only. For ease of reading we will first present a summary of warning statements relevant to lower EFA content and then the entire label.

1. Indications and Usage

(b) (4)

5.6 Monitoring/Laboratory Tests

Monitor serum triglycerides, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, and blood count, including platelets and coagulation parameters, (b) (4) throughout treatment.

(b) (4)

9.3 Tabular Listing of All Clinical Studies

Tabular Listing of All Clinical Studies in NDA 204508
Clinolipid (ClinOleic)

Study Type	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
5.3.3.1 Reports of Human Pharmacokinetic Studies								
PK	C 88 CSW 6/3 04 F	Evaluate metabolism and kinetics	Randomized, open-label, crossover, active control	ClinOleic versus Intralipid 0.1 g/kg/h IV	6 planned 6 treated 6 ClinOleic, 6 Intralipid	Healthy adult subjects	5 hours (single dose)	Complete; Full
PK	B 9208 E	Evaluate elimination of triglyceride-rich particles	Randomized, open-label, crossover, active control	ClinOleic versus Intralipid 0.1 g/kg bolus, then 0.25 g/kg/h IV	6 planned 6 treated 6 ClinOleic, 6 Intralipid	Healthy adult subjects	1 hour (single dose)	Complete; Full
PK	C 91 CSW 6/3 12 F	Evaluate biliary secretion and jejunal absorption of bile acids	Randomized, double-blind, crossover, active and placebo-controls	ClinOleic versus Intralipid versus saline 100 mL/h IV	9 planned 9 treated 9 ClinOleic, 9 Intralipid, 9 saline	Healthy adult subjects	4 hours (single dose)	Complete; Full
PK	B 9201 E	Evaluate metabolism following oral administration	Randomized, open-label, crossover, active control	ClinOleic versus IVELIP 25 g/m^2 BSA oral	6 planned 6 treated 6 ClinOleic, 6 IVELIP	Healthy adult subjects	Bolus (single dose)	Complete; Full
Study Type	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Planned Duration of Treatment**	**Study Status; Type of Report**
5.3.5.1 Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
Controlled Studies Comparing ClinOleic to Intralipid in Adult Patients								

Efficacy and Safety	C 88 CSW 6/3 01 F	Evaluate short-term tolerability and effect on membrane and fatty acid profiles	Single center, randomized, open label, active control	ClinOleic versus Intralipid 2.45 g/kg/day IV	20 planned 7 treated 4 ClinOleic, 3 Intralipid	ICU patients following abdominal surgery	5 days	Complete; Full
Efficacy and Safety	C 88 CSW 6/3 02 F	Evaluate short-term tolerability and effect on membrane and fatty acid profiles	Single center, randomized, open label, active control	ClinOleic versus Intralipid 1.3 g/kg/day IV	20 planned 27 treated 15 ClinOleic, 12 Intralipid	ICU patients following gastrointestinal surgery or multiple trauma	5 days	Complete; Full
Efficacy and Safety	C 88 CSW 6/3 05 F	Evaluate short-term tolerability and effect on membrane and fatty acid profiles	Single center, randomized, open label, active control	ClinOleic versus Intralipid 2.3 g/kg/day IV	16 planned 20 treated 11 ClinOleic, 9 Intralipid	ICU patients following gastrointestinal surgery or multiple trauma	5 days	Complete; Full
Efficacy and Safety	C 88 CSW 6/3 06 F	Evaluate short-term tolerability and effect on membrane and fatty acid profiles	Single center, randomized, open label, active control	ClinOleic versus Intralipid 2.3 g/kg/day IV	20 planned 20 treated 11 ClinOleic, 9 Intralipid	ICU patients following gastrointestinal or vascular surgery, multiple trauma or burns	5 days	Complete; Full
Study Type	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Planned Duration of Treatment**	**Study Status; Type of Report**
Efficacy and Safety	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) IV	48 planned 48 treated 24 ClinOleic, 24 Intralipid	Hospital patients requiring total parenteral nutrition	15 days to 6 months	Complete; Full

Efficacy and Safety	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 IV	50 planned 22 treated 12 ClinOleic, 10 Intralipid	Hospital or ambulatory patients requiring supplemental parenteral nutrition	26 days to 1 year	Complete; Full
Efficacy and Safety	C 90 CSW 6/3 11 F	Evaluate efficacy and safety with long-term use	Single center, randomized, open label, active control	ClinOleic versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day) IV	12 planned 3 treated 2 ClinOleic, 1 Intralipid	Hospital patients requiring total parenteral nutrition	15 days to 6 months	Complete; Full

Study Type	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	C 91 CSW 6/3 13 F	Evaluate short-term tolerability	Single center, randomized, open label, active control	ClinOleic versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day) IV	20 planned 24 treated 13 ClinOleic, 11 Intralipid	Hospital patients requiring total parenteral nutrition	5 days minimum	Complete; Full
Efficacy and Safety	CT 2402/P24/03/C	Evaluate short-term (5 days) efficacy and safety	Multicenter, randomized, double-blind, active control	ClinOleic versus Intralipid 1 g/kg/day IV	200 planned 200 treated 100 ClinOleic, 100 Intralipid	Hospital patients requiring parenteral nutrition for at least 50% of needs	5 days	Complete; Full
Controlled Studies Comparing ClinOleic to Other Lipid Products in Adult Patients								
Efficacy and Safety	CT 2402/P18/95/F	Evaluate long-term efficacy and safety	Single center, randomized, double-blind, active control	ClinOleic versus IVELIP 50 g/day IV	12-16 planned 13 treated 6 ClinOleic, 7 IVELIP	Patients requiring long-term, non-exclusive parenteral nutrition at home and/or in the hospital	90 days	Complete; Full
Efficacy and Safety	CT 2402/P19/96/G	Evaluate short-term efficacy and safety	Single center, randomized, double-blind, active control	ClinOleic versus SALVILIPID (= IVELIP) 1.5 g/kg/day IV	40 planned 44 treated 22 ClinOleic, 22 SALVILIPID	Hospital post-surgical patients requiring total parenteral nutrition	5 days	Complete; Full

Study Type	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	CT 2402/P20/96/I	Evaluate long-term safety of use in home parenteral nutrition	Single center, randomized, double-blind, active control	ClinOleic versus IVELIP 0.7-1.5 g/kg/day, 3-7 days/wk IV	20 planned 18 treated 9 ClinOleic, 9 IVELIP	Patients requiring long-term, non-exclusive parenteral nutrition at home and/or in the hospital	60 days	Complete; Full
Efficacy and Safety	CT 2402/P21/96/S	Evaluate short-term efficacy and safety in everely burned patients	Single center, randomized, double-blind, active control	ClinOleic versus Lipofundin (MCT/LCT) 1.28 g/kg/day IV	20 planned 22 treated 11 ClinOleic, 11 Lipofundin	Severely burned hospital patients requiring total parenteral nutrition	6 days	Complete; Full
Efficacy and Safety	CT 2402/P22/00/F	Evaluate long-term efficacy and safety in hemodialyzed chronic renal failure patients	Single center, randomized, double-blind, active control	ClinOleic versus IVELIP 0.7-0.8 g/kg/dialysis, 3 times/week IV	35-40 planned 41 treated 21 ClinOleic, 20 IVELIP	Chronic renal failure patients (hemodialysis at least 6 months) with moderate to severe malnutrition	35 days	Complete; Full
Controlled Study Comparing Multi-chamber Product Containing ClinOleic to No Lipid Emulsion in Elderly Patients								
Efficacy and Safety	ICS1063A/P01/01/F (study started as CT 2110/P03/01/F)	Evaluate efficacy mainly in improvement of appetite) and safety	Single center, randomized, open label, untreated control	OLICLINOMEL ersus no parenteral lipid 1000 mL/day IV	60 planned 19 treated 10 ClinOleic, 9 control	Elderly anorexic and malnourished patients requiring parenteral rehydration	7 days	Complete; Full

Study Type	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Controlled Studies Comparing ClinOleic to Intralipid in Pediatric Patients								
Efficacy and Safety	C 88 CSW 6/3 03 F	Evaluate medium-term tolerability and effect on erythrocyte and plasma fatty acid profiles	Single center, randomized, open label, active control	ClinOleic versus Intralipid 2.5 g/kg/day IV	20 planned 18 treated 8 ClinOleic, 10 Intralipid	2 month-old to 3 year-old patients with acute or chronic surgical or medical conditions requiring total parenteral nutrition	15-120 days	Complete; Full
Efficacy and Safety	CT 2402/P14/93/F	Evaluate long-term efficacy and safety	Single center, randomized, double-blind, active control	ClinOleic versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day) IV	20 planned 18 treated 9 ClinOleic, 9 Intralipid	1 to 18 year-old patients with surgical or medical conditions requiring parenteral nutrition	2 months	Complete; Full
Efficacy and Safety	CT 2402/P15/94/G	Evaluate short-term (7 days) efficacy and safety in premature infants	Multicenter, randomized, double-blind, active control	ClinOleic versus Intralipid escalating: 0.5-2.0 g/kg/day (maximum rate of 6.0 g/kg/day) IV	40 planned 42 treated 22 ClinOleic, 20 Intralipid	Premature newborns requiring total parenteral nutrition	7 days	Complete; Full

Study Type	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
5.3.5.2 Reports of Uncontrolled Clinical Studies								
Uncontrolled Study of ClinOleic in Adult Patients								
Efficacy and Safety	CT 2402/P17/95/UK	Evaluate long-term safety and efficacy in home parenteral nutrition	Single center, open label non-comparative	ClinOleic ≥ 200 g/wk, (administered at least twice per week)	10-20 planned 13 treated	Stable long-term home parenteral nutrition patients	6 months	Complete; Full
Uncontrolled Studies of Multi-chamber Products Containing ClinOleic in Adult Patients								
Efficacy and Safety	ICS1063B/ P01/03/Mu.F	Evaluate short-term efficacy and safety	Multicenter, randomized, double-blind, active control *Note: Included as an uncontrolled study because ClinOleic is the lipid emulsion in both test products.*	OLICLINISOL versus OLICLINOMEL maximum rate of 40 mL/kg/day IV	50 planned 66 treated[a] (33 per arm)[a]	Hospital patients requiring parenteral nutrition	5 days	Complete; Full
Efficacy and Safety	BX_OLCMN4_301	Evaluate ease of use; and short-term efficacy and safety	Single center, open label non-comparative	OLICLINOMEL N4550E maximum rate of 40 mL/kg/day IV	15 planned 20 treated	Hospital patients requiring parenteral nutrition	5 days	Complete; Full

Study Type	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	BX_OLCMN7_301	Evaluate ease of use; and short-term efficacy and safety	Single center, open label non-comparative	OLICLINOMEL N71000E maximum rate of 36 mL/kg/day IV	15 planned 16 treated	Hospital patients requiring parenteral nutrition	5 days	Complete; Full
Uncontrolled Study of Multi-chamber Product Containing ClinOleic in Pediatric Patients								
Efficacy and Safety	Ped3CB/P01/ 06/Mu.B	Evaluate short-term efficacy and safety; and ease of use	Multicenter, open label non-comparative	NUMETA adjusted to nutritional need IV	140 planned 159 treated	Hospital patients (pre-term newborn through 18 yr-old) requiring parenteral nutrition	5 days (up to 10 days for preterm newborns)	Complete; Full
5.3.5.3 Reports of Analyses of Data From More Than One Study								
Efficacy and Safety	C 88 CSW 6/3 01 F, C 88 CSW 6/3 05 F, and C 88 CSW 6/3 06 F: Global Analysis	Evaluate short-term tolerability and effect on membrane and fatty acid profiles	Randomized, open-label, active control	ClinOleic versus Intralipid 2.3-2.4 g/kg/day IV	56 planned 47 treated 26 ClinOleic, 21 Intralipid	Adult ICU patients following surgery, multiple trauma or burns	5 days	Complete; Full

Study Type	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
5.3.5.4 Other Study Reports								
Efficacy and Safety	Review of ClinOleic Publications	Evaluate efficacy and safety	Literature review	ClinOleic	3,837 adult 3,539 ClinOleic, 298 soy-based lipid emulsion 563 pediatric 357 ClinOleic, 206 soy-based lipid emulsion	Various patients requiring parenteral nutrition	Varying durations	Complete; Full
Safety	BE1000586 Supplemental Safety Analysis	Evaluate safety of lipid products used for parenteral nutrition in hospitals	Retrospective, multicenter, chart review	ClinOleic or OLICLINOMEL versus other lipid products any dose IV	1609 treated 838 ClinOleic or OLICLINOMEL, 771 other lipid products	Hospital patients requiring parenteral nutrition	Any duration	Complete; Full

Study Type	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Planned Duration of Treatment	Study Status; Type of Report
Safety	1994 SAE Summaries Final Report.	Some of the early clinical study reports (CSRs) did not provide narratives for patients who had SAEs. Therefore, narratives for these patients were written in 1994 and are provided in an expert report entitled 1994 SAE Summaries Final Report.	Narratives	ClinOleic versus Intralipid • 1.3 g/kg/day IV • 2.3 g/kg/day IV; or • 2.45 g/kg/day, IV *Or* ClinOleic versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day) IV	13 individual patients with SAEs or who died: 1: C 88 CSW 6/3 01 F 1: C 88 CSW 6/3 02 F 3: C 88 CSW 6/3 05 F 1: C 88 CSW 6/3 06 F 1: C 89 CSW 6/3 08 F 3: C 89 CSW 6/3 10 F 1: C 90 CSW 6/3 11 F 2: C 91 CSW 6/3 13 F	5 ICU patients following GI surgery or multiple trauma 1 ICU patient following GI or vascular surgery, multiple trauma or burns 3 Hospital or ambulatory patients requiring supplemental parenteral nutrition 4 Hospital patients requiring total parenteral nutrition	Varying durations	Complete; Full

[a] The data for the 10 patients treated at the Spanish site in this study are only included in the integrated safety analyses (refer to ICS1063B/P01/03/Mu.F, Section 10.1).

BSA = body surface area; ICU = intensive care unit; IV = intravenous; MCT/LCT = medium-chain triglycerides/long-chain triglycerides; PK = pharmacokinetics.

9.4 Exposure Duration and Dosage, Adult Comparative Studies

	9 Comparative Studies vs Intralipid		14 Comparative Studies vs All Lipids		7 Short-term Comparative Studies		7 Long-term Comparative Studies	
	ClinOleic (N=192)	**Intralipid (N=179)**	**ClinOleic (N=261)**	**Comp. (N=248)**	**ClinOleic (N=174)**	**Comp. (N=166)**	**ClinOleic (N=87)**	**Comp. (N=82)**
Duration (Days)								
n	192	179	261	247	174	166	87	81
mean (SD)	19.7 (56.9)	15.6 (41.6)	21.6 (50.9)	19.0 (38.8)	5.0 (0.8)	5.1 (0.7)	54.8 (78.5)	47.7 (58.2)
median (min-max)	5.0 (1-438)	5.0 (1-394)	5.0 (1-438)	5.0 (1-394)	5.0 (1-6)	5.0 (1-6)	34.0 (3-438)	34.0 (1-394)
Treatment Interval (n (%))								
n	192	179	261	248	174	166	87	82
1 day	1 (0.5%)	1 (0.6%)	3 (1.1%)	2 (0.8%)	3 (1.7%)	1 (0.6%)	0	1(1.2%)
2-7 days	150 (78.1%)	135 (75.4%)	184 (70.5%)	168 (67.7%)	171 (98.3%)	165 (99.4%)	13 (14.9%)	3 (3.7%)
8-15 days	13 (6.8%)	15 (8.4%)	13 (5.0%)	16 (6.5%)	0	0	13 (14.9%)	16 (19.5%)
16-30 days	13 (6.8%)	15 (8.4%)	14 (5.4%)	15 (6.0%)	0	0	14 (16.1%)	15 (18.3%)
31-60 days	5 (2.6%)	6 (3.4%)	25 (9.6%)	25 (10.1%)	0	0	25 (28.7%)	25 (30.5%)
>60 days	10 (5.2%)	7 (3.9%)	22 (8.4%)	21 (8.5%)	0	0	22 (25.3%)	21 (25.6%)
Lipid Dosage (g/kg/day)								
n	190	173	259	242	174	163	85	79
mean (SD)	1.3 (0.6)	1.2 (0.5)	1.2 (0.6)	1.1 (0.6)	1.2 (0.5)	1.2 (0.5)	1.1 (0.7)	1.0 (0.7)
median (min-max)	1.0 (0.5-3.2)	1.0 (0-2.7)	1.0 (0-3.2)	1.0 (0-2.8)	1.0 (0.6-3.2)	1.0 (0-2.6)	0.9 (0-3.1)	0.9 (0-2.7)
Energy Dosage (g/kg/day)								
n	189	173	258	242	173	163	85	79
mean (SD)	30.3 (11.5)	29.2 (12.1)	28.3 (12.2)	27.2 (12.4)	28.3 (9.0)	27.0 (9.1)	28.4 (16.9)	27.6 (17.3)
median (min-max)	28.6 (11.6-70.0)	26.2 (0.2-65.5)	28.5 (3.7-70.0)	26.0 (0.2-65.5)	28.6 (11.6-59.3)	25.9 (0.2-49.3)	28.5 (3.7-70.0)	26.2 (6.0-65.5)

9.5 Pediatric and Maternal Health Staff Review

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research Office of New Drugs - Immediate Office Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date:	July 13, 2011
To:	Helen Sile, MD, Medical Officer Robert Fiorentino, Medical Team Leader
From:	Laurie S. Conklin, MD, Medical Officer Pediatric and Maternal Health Staff
Through:	Hari Cheryl Sachs, MD, Medical Team Leader Lisa Mathis, MD, OND Associate Director Pediatric and Maternal Health Staff
Project Manager:	Denise Pica-Branco, PhD
Drug:	ClinOleic 20%
Proposed Indication:	Parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Dosage form and route of Administration:	Intravenous emulsion

Materials Reviewed:
Meeting package for Type B meeting

Consult Question: Baxter is requesting a Type B meeting to obtain agreement with the Agency on the requirements to support registration of this lipid product in the US.

DGIEP requests input regarding the Sponsor's Question: Baxter proposes that these studies satisfy the requirements of the Pediatric Rule. Does the Agency concur?

Background:
ClinOleic is an intravenous lipid containing a blend of olive and soybean oils in a 4:1 ratio. It is packaged (b) (4) and is co-administered with amino acids, dextrose and electrolytes in the administration of PN.

When lipid emulsions were first introduced in the 1960's, they were derived from soybean oil, which contains a high concentration of essential fatty acids linoleic acid (LA) and alpha-linolenic acid (ALA). LA is an omega-6 and ALA an omega-3 long chain polyunsaturated fatty acid (LCPUFA). Commercially available lipid emulsions for use in the US are soybean oil emulsions. Some studies have suggested that use of soybean oil emulsions in the intensive care may be associated with increased rates of infection and sepsis, due to affects on neutrophil migration and lymphocyte apoptosis.[2,3] The clinical data, however, are contradictory regarding this risk, however, as some studies have shown no association between soybean oil emulsion and increased risk of infection. [4] There are no prospective randomized trials that demonstrate a clear relationship between the use of soybean oil emulsions and infection. Despite this, the Society of Critical Care Medicine and American Society of Parenteral and Enteral Nutrition (ASPEN) have issued guidelines for nutrition support of critically ill adult patients in 2009, recommending not administering PN with soybean oil-based lipid emulsion during the first week of hospitalization, based upon evidence suggesting pro-inflammatory and immunosuppressive effects, and possible increased risk of morbidity and mortality. [5] Thus, this is an important unanswered clinical question.

The high number of double bonds found in LCPUFA's are associated with an increased risk of oxidative stress and increased lipid peroxidation, perhaps playing a role in the development of sepsis and multi-organ failure.[6, 7, 8,9,10] Administration of soybean-oil-based lipid emulsions are also associated with high blood levels of omega-6, a higher derivative of linolenic acid, and its metabolite, arachadonic acid (AA). The metabolism of AA can produce pro-inflammatory eicosanoids (prostaglandins, thromboxanes, and leukotrienes), that regulate other inflammatory mediators .[11] Subsequent development of lipid emulsions has been focused on replacing soybean oil (omega-6 fatty acids) with other oils, including coconut oil (rich in medium chain triglycerides), olive oil (rich in omega-9 fatty acid) and fish oil (omega-3 fatty acids). [12]

ClinOleic was developed to provide an intravenous lipid emulsion with a lower proportion of LCPUFA's than that found in soybean oil emulsions. Although the advantages of an olive oil emulsion have not been demonstrated conclusively, possible advantages of olive oil emulsion include:

- Olive oil emulsions contain more monounsaturated fatty acids (MUFAs) which are potentially more resistant to peroxidation and may have additional anti-inflammatory effects.[13]
- In vitro studies have suggested that there may be fewer effects on lymphocyte activation and apoptosis with olive oil LE than with soybean oil.[14,15] A reduced incidence of infectious complications was seen in severely burned ICU patients administered olive oil lipid emulsion within PN.[16]
- Olive oil emulsions are hypothesized to have less of an effect on effect upon lipid peroxidation and inflammation.

Regulatory Background:
Although unapproved in the U. S., Baxter has received authorization to market ClinOleic in multiple countries worldwide, including Canada, Australia, and within the European Union. To support their NDA, Baxter plans to submit existing preclinical and clinical data from eighteen Baxter-sponsored clinical trials (15 in adults and 3 in pediatric patients) that have been conducted worldwide.

Baxter intends to file a 505(b) (1) NDA for ClinOleic, as indicated for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. In addition, Baxter plans to register a portfolio, containing two other triple chamber bags (Olimel for adults and Numeta for children) containing ClinOleic as the lipid source. Triple chamber bags (also called 3-in-1 solutions or total nutrient admixtures) are solutions in which the lipid emulsion is mixed with the amino acid/glucose solution and administered through a single line. This method of delivery offers the advantage of simplified administration (with possible cost savings), less manipulation of the delivery system (with potential reduced opportunity for contamination), and continuous infusion of all nutrients. Numeta is a triple chamber IV bag: one chamber contains ClinOleic, a second chamber containing electrolytes and a third contains an amino acid product called Primene, which is not approved in the US.

Two investigator-initiated IND's have been opened in the US:
1) IND 105935: a study to assess the clinical and physiologic response of adult patients with the Acute Respiratory Distress Syndrome to supplemental ClinOleic;
2) IND 079616: a study in adults evaluating the effects of ClinOleic on endothelial function inflammation, neutrophil function, oxidative stress, immune function, and insulin resistance in healthy adults. A second trial under the same IND proposes to evaluate whether ClinOleic emulsion will decrease the incidence of nosocomial infections, intensive care unit and hospital length of stay, as well as other immune system markers.

Dosing:
According to guidelines for use of parenteral nutrition in children and adults, lipid intake should generally not exceed 3 g/kg/day or 50% of energy intake. Failure to provide at least 2% to 4% of the total caloric intake as LA and 0.25% to 0.5% of the total caloric intake as ALA may lead to a deficiency of these two essential fatty acids. Manifestations

of essential fatty acid deficiency can include alterations in platelet function, hair loss, poor wound healing and dry, scaly skin. [1] Commercially available soybean emulsion contains approximately 55-60% of total calories as LA and 3-4% of calories as ALA.[1]

Studies Supporting Efficacy:

Baxter intends to submit the following clinical data in support of the proposed indication:

- Data from 15 ClinOleic clinical trials and 3 additional clinical trials evaluating triple-chamber combination products containing ClinOleic emulsion in adults (see Appendix)
- Efficacy and safety data in pediatric patients from 3 ClinOleic trials and 1 additional trial evaluating a triple-chamber product (Numeta) containing ClinOleic as the lipid source
- A cumulative summary of Periodic Safety Update Reports for the ClinOleic product in the EU and rest of the world that covers 15 years of market experience
- A cumulative summary of supporting data from completed and ongoing investigator-initiated trials evaluating the ClinOleic emulsion in the US
- A cumulative summary of scientific journal articles evaluation adult and pediatric patients exposed to ClinOleic and published over the period of 1992 through 2010

In support of efficacy in pediatrics, Baxter has submitted a brief summary of 3 pediatric studies:

Study Number	Description of Study	Subjects	Type of study	Clin Oleic Dose	Efficacy Endpoint (per Sponsor's packet)
C88CSW 6/3 03F	Tolerability and efficacy of emulsion in children	18 infants enrolled, 16 analyzed, 9 in treatment arm (ages 2-57 months)	Randomized, open-label, comparative study in subjects with chronic medical disorders (refractory severe diarrhea) or acute surgical disorders (some requiring ileostomy) receiving Clin Oleic or Intralipid	2.9 g/kg/day mean 17 days	Analysis of plasma phospholipid fatty acid composition, EFA's, total protein levels
CT2402/P 14/93/F	Long term efficacy and safety of ClinOleic 20% compared to Intralipid in Children and Teenagers	20 subjects enrolled, 18 analyzed subjects, 9 in treatment arm (ages 1-9)	Prospective, controlled, randomized, double-blind trial that evaluated the administration of ClinOleic or Intralipid in children	1.92 g/kg/day, mean 56 days	Plasma phospholipid fatty acids, Clinical nutritional parameters (i.e. height and weight) and albumin levels.
CT2402/P 15/94/G	A Phase 3, Prospective, Randomized, Multicenter Study of the Safety and Efficacy of ClinOleic 20% IV Fat Emulsion in Premature Children	45 infants enrolled, 33 analyzed subjects, 18 in treatment arm (gestational age 28-36 weeks)	Prospective, randomized, double-blind trial	1.46 g/kg/day, duration of 6 days	Change in omega-6 fatty acids

Reviewer Comments: Most of the adult studies were short-term studies in critically ill patients. In addition, 9 studies were open-label. The sufficiency of the adult and preclinical studies is deferred to the division. However, the pediatric studies appear to have several potential weaknesses based on the summaries provided:

- *Study C88CSW 6/3 03F was published in 1996, prior to the ICH Good Clinical Practice Guidance (E6), which was published on May 9, 1997.*
- *The dose of ClinOleic used in CT2402/P15/94/G was less than the recommended 2 g/kg/day.*
- *The length of treatment was relatively short, with only one of the 3 trials enrolling patients for > 1 week.*
- *The Sponsor acknowledges that different endpoints were used in these studies, and that endpoints used for nutritional assessment may be affected by underlying disease and the age of the patients (i.e. growth may be a good indicator of nutritional status in a preterm infant, but not in an adult patient following surgery).*
- *Only one of the trials (CT2402/P14/93/F) examined clinically relevant endpoints such as growth. The summaries do not adequately describe if a the studies comprehensively examined the range of relevant endpoints (fatty acid levels, albumin, glucose, electrolytes, kidney and liver function, growth, coagulation studies, essential fatty acids).*
- *Overall, very few children were treated with ClinOleic in these trials (9, 9, and 18 subjects respectively).*
- *The Sponsor appears to be relying on limited data in pediatric patients and would likely be extrapolating efficacy in adults. Generally, extrapolation of efficacy from two adequate and well-controlled studies in adults may be possible in pediatrics if there is a similar course of disease and a similar exposure-response. PMHS believes that the condition of requiring parenteral nutrition "when oral or enteral nutrition is not possible, insufficient, or contraindicated" is similar between adults and children. The Division must feel comfortable that efficacy has been adequately demonstrated in adults before extrapolation could be considered. If extrapolation is used, a rationale must be documented within the review.*
- *Even when extrapolating efficacy from adults to pediatric patients is appropriate, supportive data is needed for effectiveness, dosing and safety. Since pharmacokinetic data is not available, a study with clinical efficacy endpoints appears to be needed to support dosing and safety, particularly in a growing child. Longer term studies in children are necessary to demonstrate safety in all age groups. It should be demonstrated by the Sponsor that adequate daily doses of ALA and LA will be provided by ClinOleic. Demonstration of adequate essential fatty acid levels is necessary.*

Adverse Events and Safety:

Notably, adverse events (AE's) for the 3 clinical studies evaluating ClinOleic were "not summarized across studies" and were not presented. The most comprehensive study to

evaluate safety in the pediatric population was the noncomparative study of Numeta, a combination product containing ClinOleic and an amino acid source (Primene) that is not approved in the US.

Numeta	Ped3CB/P01/06/Mu.F	Short-to-mid-term	Open-label	Premature infants, term infants and toddlers, children/adolescents requiring PN	None	159 pediatric patients

Numeta was administered at a weight based dose (adapted to the patient's needs) for 5 days. Preterm newborn infants could have been treated for up to 10 days. A total of 115 preterm infants, 28 term/toddlers and 18 children/adolescents were enrolled in the study. A total of 207 treatment-emergent adverse events (AE's) were reported in 105 subjects. In preterm infants, the most commonly reported AE's were hyperglycemia, anemia, sepsis, hyponatremia, and constipation. In term infants/toddlers, the most commonly reported AE's were pyrexia and hyperglycemia. In children/adolescents, the most commonly reported AE's were vomiting, pyrexia, and constipation.

Reviewer comment: The long-term safety data in children are uncontrolled. These adverse reactions would not be unexpected in a critically ill or neonatal population. However, they do differ slightly from those observed in adults.

Baxter reports that in adults, the most common treatment-emergent AE's were elevated hepatic enzymes (4% ClinOleic; 3.8% soybean oil emulsion) and elevated neutrophil counts (4% ClinOleic, 2.1% soybean oil emulsion). Incidence of AE's, serious AE's and deaths in adults were comparable between ClinOleic and soybean oil-based emulsions.

In addition to the clinical studies reviewed, Periodic Safety Update Reports from November 1995 through April 2009 indicated that (b) (4) units of ClinOleic have been sold worldwide, translating to approximately 1 million patients exposed to ClinOleic in the post marketing setting (according to Baxter).

Reviewer Comment: No information is provided regarding what percentage of these 1 million patients were children.

Published Literature in Support of the Application

Adult studies: Baxter intends to submit 17 articles published between 1992 and 2010, including a total of 291 patients. 13 were comparative studies between patients who received ClinOleic versus some other lipid emulsion (soy, SMOF, MCT/LCT structured lipids). Endpoints were different among studies and included: BMI, albumin, hematology, septic episodes, mortality, hospital length of stay, ICU length of stay, liver function tests, mean heart rate, central venous pressure, catheter infections, other infections, unplanned admissions, thrombotic episodes, adverse events, hemofilter longevity, organ failure, duration of ventilation, respiratory quotient, and inflammatory markers. Eight studies evaluated metabolic effects, including serum triglycerides,

cholesterol, and glucose. Overall, Baxter states that all 17 studies demonstrated "no significant differences in clinical outcome, safety, or serum inflammatory marker levels between patients who received ClinOleic and those who received MCT/LCT, or structured lipid emulsions.

Reviewer comment: The ability of the adult literature to support approval is deferred to the division.

Pediatric studies: A total of 10 pediatric literature- based studies (1996 through 2009) are being submitted by Baxter. All were comparative studies between patients receiving ClinOleic vs. another lipid formulation (soy or MCT/LCT). These studies evaluated a total of 322 patients. Exposure time ranged from 5 to 56 days. Patients exposed ranged from preterm infants <37 weeks gestational age to 18 years of age. Like the adult studies, outcomes are variable, including anthropomorphic parameters, liver function tests, BUN, electrolytes, total and conjugated bilirubin, bile acids, coagulation studies, necrotizing enterocolitis, incidence of bronchopulmonary dysplasia, and intraventricular hemorrhage. Seven studies reported inflammatory markers as a study outcome. Eight studies reported metabolic effects, such as levels of alpha-tocopherol, HDL levels, LDL levels, and vitamin E status. Baxter again concludes from these studies that there were no significant clinical outcome or safety differences between ClinOleic and soybean oil-based lipid emulsions in pediatric populations.

Reviewer Comment:

- *Three of the 10 submitted literature-based studies in pediatrics were already submitted by Baxter (C88CSW 6/3 03F, CT2402/P14/93/F, and CT2402/P15/94/G) (discussed above). Thus, there are really only 7 literature-based studies submitted.*
- *As discussed above, study C88CSW 6/3 03F was published in 1996, prior to the ICH Good Clinical Practice Guidance (E6), which was published on May 9, 1997.*
- *This data is supportive only.*

PMHS Recommendations:
In order to extrapolate efficacy to the pediatric population, the primary division must be comfortable that there are 2 adequate and well-controlled studies in adults supporting dosing, safety, and efficacy. (b) (4)

- Studies must be performed in children using adequate and consistent dosing of lipids (2-3 g/kg/day).
- Studies will need to address the full age span (preterm and term neonates, toddlers, children, and adolescents).
- If efficacy cannot be extrapolated, studies in pediatric patients must demonstrate growth and adequate maintenance of nutritional parameters (anthropomorphic

measurements, prealbumin, hemoglobin, essential fatty acids, fat soluble vitamin levels)

- Additional long- term safety data is needed in a sufficient number of patients. Careful attention must be paid to monitoring of essential fatty acids, coagulation studies, transaminases, fat soluble vitamins, triglyceride levels, and lipid profiles.

Proposed Answer to Sponsor's Question: Baxter proposes that these studies satisfy the requirements of the Pediatric Rule. Does the Agency concur?

PMHS Suggested Response:
Because FDA' s Pediatric Rule at 21 CFR 314. 55 and 21 CFR 601.27 was challenged and overturned in court, FDA was not allowed to enforce these provisions. Under PREA (2007), a pediatric assessment is required for NDA/BLA or supplements with a new active ingredient, indication, dosage form, dosing regimen, or route of administration. The CMC reviewer (Marie Kowblansky) has determined that olive oil is not a new active ingredient, based on the following factors:
1) The USP definition of Lipid Injectable Emulsion allows for the use of olive oil and other oils in combination with soy oil.

> *Lipid Injectable Emulsion: 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 oil(s). It contains no antimicrobial agents. The final products are terminally sterilized.*

Since this proposed product is a 4:1 ratio of olive: soy oil, it conforms to the above definition and would not be considered a new molecular entity, new active ingredient, or new dosage form.

2. The fatty acid components of olive oil are the same as in soy oil, just the proportions are different.

Thus, with the current sought indication, this formulation does not appear to trigger PREA.

Appendix I: Controlled studies in adults intended to support efficacy

Adult trials with ClinOleic acid only

	Study #	Duration	Blinding	Populations	Comparator	Exposure
Clin Oleic	C88CSW 6/3 02F	Short-term	Open-label	ICU patients given ≥ 6 days of TPN for multiple trauma or surgery	Intralipid	15 adults

	C88CSW 6/3 01F	Short-term	Open-label	ICU patients given ≥ 6 days of TPN for multiple trauma or surgery	Intralipid	4 adults
	C88CSW 6/3 05F	Short-term	Open-label	ICU patients given ≥ 6 days of TPN for multiple trauma or surgery	Intralipid	11 adults
	C88CSW 6/3 06F	Short-term	Open-label	ICU patients given ≥ 6 days of TPN for multiple trauma or surgery	Intralipid	11 adults
`	C91CSW 6/3 13F	Short- to mid-term	Open-label	ICU patients given ≥ 5 days of TPN for multiple trauma or surgery	Intralipid	13 adults
	CT2402/P19/96/G	Short-term	Double-blind	ICU patients (non-septic) given ≥ 5 days TPN post-GI surgery	Intralipid	22 adults
	CT2402/P21/96/S	Short-term	Double-blind	Hospitalized patients needed ≥ 5 days TPN for severe burns	Lipofundin	11 adults
	CT2402P24/03C	Short-term	Double-blind	Hospitalized patients needed ≥ 5 days PN representing at least 50% of daily needs	Intralipid	100 adults
	C89CSW 6/3 08F	Mid-term	Open-label	Medical or surgical pathology requiring TPN (oral intake < 10%) for ≥ 15 days (up to 6 months)	Intralipid	24 adults
	C90CSW 6/3 11F	Short-term	Open-label	ICU patients administered TPN for ≥ 15 days	Intralipid	2 adults
	C89CSW 6/3 10F	Short-term	Open-label	Medical or surgical pathology requiring long-term PN to supplement oral intake	Intralipid	12 adults
	CT2402/P18/95F	Long-term	Double-blind	Functional intestinal failure; home PN with 1 month washout and 3 month treatment period	Ivelip	6 adults
	CT2402/P20/96/I	Long-term	Double-blind	Short-bowel syndrome or intestinal failure; home PN with 1 month washout and 2-month treatment period	Ivelip	9 adults
	CT2402/P22/00F	Mid-term	Double-blind	Hemodialysis patients with chronic renal failure and moderate to severe malnutrition	Ivelip	21 adults
	CT2402/P17/95/UK	Long-term	Open-label	Chronic, stable intestinal failure patients; home PN with a 15 day washout and 6 month treatment period	None	13 adults

Adult trials using combination products that contain ClinOleic:

Olimel	BX_OLCMN4_301	Short-term	Open-label	GI surgery patients requiring PN for at least 5 days	None	20 adults
OliClinomel	BX_OLCMN7_301	Short-term	Open-label	GI surgery patients requiring PN for at least 5 days	None	17 adults
Olimel	ICS 1063B/P010/03 Mu.F	Short-term	Double-blind	Patients with any pathology requiring balance PN representing at least 50% of daily energy needs	OliClinomel	56 adults

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/s/

LAURIE S CONKLIN
07/14/2011

HARI C SACHS
07/18/2011
I concur. Since this product will likely be used off-label in pediatric patients, a WR should be considered.

LISA L MATHIS
07/18/2011

9.5 Letter from Dr. Richard Ostlund, Washington University, St. Louis, MO, concerning the proposed Phytosterol Post-Marketing Requirement

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Washington
WASHINGTON·UNIVERSITY·IN·ST·LOUIS
School of Medicine

Richard E. Ostlund Jr., M.D.
Professor of Medicine
Division of Endocrinology,
Diabetes and Metabolism

September 8, 2013

Dr. Klaus Gottlieb
FDA
Division of Gastroenterology and Inborn Error Products
10903 New Hampshire Ave
Bldg 22 Room 5204
Silver Spring, MD 20993-0002

Dear Dr. Gottlieb,

I have read the summary paper that you sent me by E-mail on June 6, 2013 entitled "Review of Publications on Parenteral Nutrition-associated Liver Disease and the Role of Phytosterols." My response addresses your specific questions found in the same E-mail.

Overall, the review seems to be balanced and presents the idea that parenteral lipid preparations that contain lower levels of phytosterols might carry benefits. Inconsistencies in the data are fairly pointed out in the text and discussed. However, in the conclusion section the review states on p. 58 that "Baxter believes that providing a lipid emulsion product with a lower phytosterol content than current US-approved soybean oil-based lipid emulsions offers a major improvement in PN for all patients..." While I agree that reduced toxicity with ClinOleic compared to other soybean-based emulsions is a possibility, I disagree that it has been established with enough certainty to be used in clinical decision making. Certainly, in my opinion, this should not be used in marketing or health claims based on current data.

I would very much like to see a really good study of the role of phytosterols in PNALD. The study you suggest, reducing phytosterol content in the oil and keeping everything else the same, is just what needs to be done. I enthusiastically support it. If you just switch oils (i.e., soybean to fish oil), there will always be questions about what aspects of the oils cause differences in PNALD. There are differences both in fatty acid content and in amounts of trace components, including but not limited to phytosterols. Trying to make any kind of credible scientific argument in favor of reduced phytosterols by comparing ClinOleic (with a 37% reduction in phytosterols) with current soybean-based parenterals of different fatty acid content is hopeless. The only experiments that would be helpful are those in which there is only one variable, the phytosterol content, and where differences in this variable are large.

The experiment I envision would not even need to involve ClinOleic. It could simply be two specially-prepared, non-commercial lipid emulsions, one made with soybean oil (or

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any other suitable oil mixure) and one with phytosterol-deficient oil but otherwise identical.

There are several readily-available technologies to reduce phytosterol content in oils. In an academic lab we have made about 100 kg of sterol-reduced soybean oil for feeding studies using charcoal adsorption (see Racette SB, Lin X, Lefevre M, Spearie CA, Most MM, Ma L, Ostlund RE Jr. 2009. Dose effects of dietary phytosterols on cholesterol metabolism: a controlled feeding study. Am. J. Clin. Nutr. 91:32-38.) Although we are very proud of this study, I don't recommend it as an industrial paradigm. Our greatest difficulty was lack of access to proper industrial equipment. This is not a limitation for Baxter or other manufacturers.

Before detailing some methods that could be used to make phytosterol-deficient oils, let me call your attention to the high level of expertise that exists with respect to food oil purification today in the United States and worldwide. The American Oil Chemists Society (AOCS) is a hundred-year old group that consists of industrial, governmental and academic scientists who share information about food oils and lipid processing. For example, there is a short course on industrial purification of soybean oil with emphasis on derived sidestream products such as lecithin, phytosterols and vitamin E. The soybean oil that is used for Intralipid is already refined before entering production. The question is how the refining process could be changed to yield phytosterol-deficient oils. Currently a phytosterol-deficient oil is seen as a poor product since phytosterols may confer cardiovascular benefits. Operationally Baxter could have one of its employees who may already be a member of AOCS contact knowledgeable process engineers at Cargill or ADM (the largest soybean oil producers.) These oil suppliers work with customers to develop new products and would likely be extremely interested in providing a high-value-added specialty oil that could be used in parenterals. They actively seek such relationships because bulk food oil provides very little profit. From FDA's point of view, it would be important to improve the purity of lipid emulsions. All the components are in place for this to happen.

I would envision that Baxter and, say, Cargill (the country's second largest soybean processor), would jointly produce small quantities of high-quality soybean oil that could be used in a clinical trial in expectation of a larger market depending on the results of the trial.

Here are examples of ways to produce phytosterol-deficient soybean oil.

1. Vacuum Distillation. Currently vitamin E and some phytosterols are produced by vacuum distillation of soybean oil. The residual oil would be phytosterol-reduced.
2. Supercritical carbon dioxide extraction of oils. In this technique liquid carbon dioxide is used as a solvent to extract phytosterols.
3. Steam distillation of oils. Passage of steam through an oil over short time periods removes phytosterols while leaving the triglyceride behind and not greatly affecting the oil. This technique is used to remove vitamin A (red

color) and phytosterols from crude palm oil and is well established industrially.

4. Resynthesis of triglycerides from pure fatty acids. The original ClinOleic oil is hydrolyzed to free fatty acids, the fatty acids are separated from phytosterols and other contaminants, and the fatty acids are resynthesized to triglycerides. In the future, commercial pure free fatty acids could be purchased to provide a synthetic, phytosterol-free starting material. This would be the most ideal parenteral component.

The removal of phytosterols has one problem that has to be addressed. Oils contain both free phytosterols (which are more polar than triglycerides) and also esterified phytosterols (which are less polar than triglycerides). So separation methods need to consider both phytosterol forms. Technique #3 above would convert all the phytosterols into the free form, which are separable from fatty acids in one step.

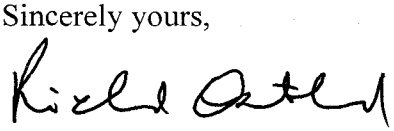
Specific questions:

1. Clinical trial design: The study might be done with two specially-prepared parenteral lipid emulsions. This might be soybean oil and soybean oil that is at least 80% reduced in phytosterols. You want a large difference in phytosterol content (not just 37%), and this is relatively easy to achieve. It would be a randomized, double-blind trial. The primary endpoint would be cholestasis with secondary clinical endpoints that include phytosterol and phytosterol/cholesterol levels in plasma.
2. Other data: It would be important to measure plasma phytosterols and cholesterol and to compute the phytosterol/cholesterol ratio. You can't make firm conclusions about phytosterols if you don't measure them, and the assays are readily available. Since fat-soluble vitamins would be extracted, the experimental design would have to include a way to supply them. You might want to measure vitamins A, D, and E, or you might decide this is redundant if they are being supplemented. All of these assays can be done on very small amounts of plasma if needed, such as less than 10 microliters.
3. I see no relationship between phytosterols and essential fatty acid levels.

I hope these comments are helpful. I really believe that FDA can be helpful by suggesting clinical studies that have the potential to change outcomes.

If you need more information, please call me at 314-362-3516.

Sincerely yours,



Richard E. Ostlund MD
Director, Core Laboratory for Clinical Studies
Division of Endocrinology, Diabetes and Lipid Research
660 South Euclid Ave.,St. Louis, MO 63115

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KLAUS T GOTTLIEB
09/20/2013

ROBERT FIORENTINO
09/20/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204-508 **Applicant: Baxter** **Stamp Date: January 13, 2013**

Drug Name: ClinOleic 20% **NDA/BLA Type:505(b)2**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	✓			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	✓			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✓			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	✓			
5.	Are all documents submitted in English or are English translations provided when necessary?	✓			
6.	Is the clinical section legible so that substantive review can begin?	✓			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	✓			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	✓			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	✓			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	✓			
11.	Has the applicant submitted a benefit-risk analysis for the product?	✓			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)2 RLD= Intralipid
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			✓	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:	✓			Yes, however, none of the 16 studies submitted for the efficacy analysis can be considered "pivotal"

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			N/A	See comment above, there are no studies which the clinical or statistical TL consider pivotal
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			N/A	See comment above, there are no studies which the clinical or statistical TL consider pivotal
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	✓			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	✓			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			N/A	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	✓			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?				The database for long-term administration is small.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	✓			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	✓			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	✓			There are some emerging safety issues that were not completely addressed
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	✓			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			N/A	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	✓			Results of 3 pediatric studies were submitted
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			N/A	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	✓			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✓			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	✓			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			N/A	
34.	Are all datasets to support the critical safety analyses available and complete?	✓			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	✓			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✓			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	✓			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?		✓		Missing or incomplete
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✓			Some studies were performed prior to promulgation of GCP guidelines but according to local ethics guidelines

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.
N/A

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Klaus Gottlieb	4 February 2013
Reviewing Medical Officer	Date
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KLAUS T GOTTLIEB
03/04/2013

ROBERT FIORENTINO
03/04/2013