

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204508Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 03, 2013
From	Robert P. Fiorentino, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA # 204508
Applicant	Baxter Healthcare Corporation
Date of Submission	January 03, 2013
PDUFA Goal Date	October 03, 2013 (includes 3-month extension based on major amendment received 06/07/2013)
Proprietary Name, Established (USAN) names	CLINOLIPID, 20% lipid injectable emulsion
Dosage forms / Strength	20% Lipid Injectable Emulsion
Proposed Indication(s)	CLINOLIPID 20% Lipid Injectable Emulsion, USP, is indicated in adults for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. As a lipid emulsion, CLINOLIPID 20% provides a source of calories and essential fatty acids for adult patients requiring parenteral nutrition.
Recommendation	Approval

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1. Introduction

Baxter Healthcare Corporation submitted a 505(b)(2) NDA#204508 on January 03, 2013 for Clinolipid 20% Lipid Injectable Emulsion. The listed drug is Intralipid 20% (a 20% Intravenous Fat Emulsion). A Priority review designation was granted for this application, in part due to ongoing shortages of Intralipid 20%, the only IV lipid emulsion marketed in the U.S. at time of this NDA review. A solicited Major Amendment was received on June 07, 2013 that resulted in a 3-month review extension with a PDUFA goal date of October 03, 2013. Reader should note that in my review, “Clinoleic” is the same product as “Clinolipid.”

The following review disciplines provided reviews for this submission or are discussed within my review:

Clinical

- Klaus Gottlieb, MD, MS, MBA, review signed 9/20/2013

Clinical Pharmacology

- Kristina Estes, Pharm.D., review signed 07/26/2013

Statistics

- Behrang Vali, filing review only (NAI), signed 02/05/2013

Non-clinical

- Dinesh Gautam, Ph.D., signed 08/08/2013

CMC

- Tarun Mehta, signed 06/20/2013, addendum signed 10/02/2013

Microbiology

- Denise A. Miller, signed 06/11/2013

Division of Medication Error Prevention and Analysis (DMEPA)

- Proprietary Name Reviews
 - Denise V. Baugh, PharmD, BCPS, 06/20/2013
 - Lisa V. Khosla, Pharm.D., M.H.A., 09/06/2013
- Label, Labeling and Packaging Review
 - Denise V. Baugh, PharmD, BCPS, signed 07/12/2013

Pediatric and Maternal Health Staff

- Leyla Sahin, M.D. (Maternal Health), review signed 09/09/2013
- Alyson Karesh, M.D. (Pediatric Health), review signed 09/09/2013
- Laurie S. Conklin, MD (Pediatric Health), PMHS Consult review signed 07/18/2011 under IND#74881

Office of Prescription Drug Promotion (OPDP)

- Meeta Patel, PharmD, review signed 08/27/2013

SEALD: Director Sign-Off Review of the End-of-Cycle Prescribing Information

- Jeanne M. Delasko, signed 10/03/2013

Center for Devices and Radiological Health (CDRH)

- Jason To, Biomedical Engineer, Office of Device Evaluation, General Hospital Devices Branch reviews dated 03/05/2012[2013, date error], 06/10/2013, 07/31/2013 & 09/30/2013 (entered by Matt Brancazio into DARRTS on 5/20/2013 & 08/01/2013 & 10/01/2013)
- QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID consult review signed 09/27/2013

2. Background

The primary goals of parenteral nutrition are to supply patients with adequate energy and essential nutrients. IV lipid emulsions alone or as part of a parenteral nutrition program (with carbohydrates and amino acids) are intended for patients with gastrointestinal dysfunction, who lack the capacity to absorb adequate nutrients to maintain or recover body mass and function and cannot tolerate oral or enteral feeding. Lipids decrease the requirement for high-dose glucose, which contributes to hyperglycemia in critically ill, diabetic, and other stressed patients. Lipids also supply the patient with essential fatty acids (EFA), (fatty acids that the patient cannot synthesize). 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.

Intralipid was the first IV lipid emulsion to gain marketing approval as a 10% lipid solution in 1975 and as a 20% solution in 1981. It should be noted that 10%, is now rarely used because adverse events are more likely after administration of a 10% fat emulsion formulation than a 20% formulation, attributed to evidence that suggests the higher concentration of free phospholipid in the 10% formulation interferes with lipoprotein lipase activity (J. M. Mirtallo et al. 2010). Clearance of 20% IVFE is faster than that of 10% IVFE, purportedly due to its relatively lower concentration of free phospholipids and its larger particle size.

The proposed Clinolipid formulation is the same as the applicant's globally marketed formulation of "ClinOliec 20% Injectable emulsion" that has been available since 1995. Clinolipid 20% is an IV lipid emulsion that contains olive oil and soy oil in a 4:1 ratio.

3. CMC / Device

It should be noted that from the ONDQA perspective (review dated 10/02/2013), this NDA was recommended for approval, with an expiration dating period of 18 months, with PMR/PMCs as detailed in Section 12 below.

There are four DMFs supporting the Clinolipid NDA: DMF # 25619 for refined soybean oil, #25620 for refined olive oil, (b) (4). The DMFs were found adequate by CMC at the time of this review.

Clinolipid 20% Lipid Injectable Emulsion, USP, is packaged in (b) (4) container closure system "CLARITY" ((b) (4) PL 2401-1) made from polyolefin (b) (4) plastic (DMF (b) (4)). The drug product is a sterile, nonpyrogenic lipid emulsion comprising a mixture of refined olive oil and refined soybean oil in an approximate ratio of 4:1 (olive oil: soy oil). The pH range of the dosage form is 6.0 – 9.0.

As noted in the CMC review, based on the USP definition of a lipid injectable emulsion, the olive oil will not be considered as NME for the proposed drug product.

Table 1. Clinolipid drug product composition

Component	Quality Standard	Function	Component Quantity per 1000 mL ¹
Soybean Oil	USP	Active Pharmaceutical Ingredient	40 g ²
Olive Oil	NF	Active Pharmaceutical Ingredient	160 g ²
Glycerin	USP	(b) (4)	22.5 g
Sodium Oleate	In-house		0.30 g
Egg Phospholipids	NF		12 g
Sodium Hydroxide ³	NF	pH adjuster	(b) (4)
(b) (4)			
Water for Injection	USP	(b) (4)	(b) (4)

USP: United States Pharmacopeia; NF: National Formulary

¹ Labeled volume 1000 mL, fill volume (b) (4)² The lipid emulsion contains Olive Oil, NF and Soybean Oil, USP in a ratio corresponding respectively to approximately 4:1. The respective proportions of Olive Oil and Soybean Oil are adjusted as a function of the content of essential fatty acids in the raw material (b) (4)³ Sodium Hydroxide, NF is used to prepare a (b) (4) solution for use as a pH adjuster.

With regard to the drug substances, the following table from the CMC review compares the composition of olive oil and soy oil shows same fatty acids in slightly different concentrations.

Table 2. Comparison of Fatty Acid Concentrations between Olive Oil and Soy Oil

Fatty acid	Carbon chain length	Number of double bonds	Olive Oil	Soy Oil
palmitic	16	0	7.5 – 20.0%	9 – 13%
palmitoleic	16	1	< 3.5%	< 0.3%
stearic	18	0	0.5 – 3.5%	2.5 – 5%
oleic	18	1	56 - 85%	17 – 30%
linoleic	18	2	9 - 13%	48 – 58%
linolenic	18	3	< 1.2%	5 – 11%
arachidic	20	0	< 0.5%	< 1.0%
eicosenoic	20	1	< 0.4%	< 1.0%
behenic	22	0	< 0.2%	< 1.0%
lignoceric	24	0	< 0.2%	< 0.5%
erucic	22	1	---	< 0.3%
myristic	14	0	---	< 0.2%

Source: Adapted from CMC review dated 06/20/2013, page 25/70.

Note from Table 2 that olive oil has less of the n-6 essential fatty acid, linoleic acid, than soy oil (up to 13% vs. 58%, respectively).

The applicant has classified sodium oleate as a novel excipient, however, as noted in the CMC review, this excipient is a sodium salt of oleic acid, which is major portion of the drug substances and hence not a novel excipient.

Facilities review/inspection

The manufacture of the finished product (mixing, filling, (b) (4), packaging, labeling and control operations) is performed at a Baxter facility in Belgium. Two other sites in Belgium perform additional testing and (b) (4).

Manufacturing inspections of these three sites were completed and found to be acceptable.

Container Closure System

The proposed container closure system for the drug product is similar to those used for the approved NDAs 20678 and 20734. The detailed review of the container closure is provided in DMF (b) (4) “Baxter CLARITY” bags, which is owned by the same applicant of this NDA.

Because of concern about any potential future changes of container closure system, which had been conveyed to the applicant on March 22, 2013, the applicant agreed to a postmarketing agreement via an amendment dated, May 6, 2013. As described by the CMC reviewer, in the absence of release specification of the Clarity container closer system, the applicant will establish the change control protocol through a supplement for the monitoring any future changes in the container closure’s manufacturing process and/or any raw material.

Twist-Off Protector (TOP) Dislodgement Evaluation

During the review FDA became aware of a Health Canada Advisory posted on July 16, 2013 indicating the potential of the “presence of particles from the administration port material” for Clinoleic 20% (i.e., Clinolipid marketed in Canada)¹:

Baxter Corporation has recently received product complaints in Canada for full detachment of the sterile blue membrane in CLINOLEIC 20% emulsion after spiking with a transfer or administration set.

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

¹ <http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/34659a-eng.php> , last accessed September 18, 2013

In addition, the Health Canada Advisory provides the following recommendations to mitigate any potential risks:

According to ASPEN 2004 Guidelines on Safe Practices for Parenteral Nutrition the use of 1.2 micron in-line filtration for PN formulations with lipids is recommended to remove particulate matter and micro-precipitate contamination. Baxter recommends following the ASPEN Guidelines for PN formulations containing CLINOLEIC 20%. If you are using an administration set without a 1.2 micron filter, it is recommended to add the 2H8603 Clearlink 1.2 micron filter Extension Set or 2C1103 Interlink 1.2 micron filter Extension Set to the set. If you use a non-Baxter administration set without a 1.2 micron filter, please consult the manufacturer for appropriate options to include a 1.2 micron filter.

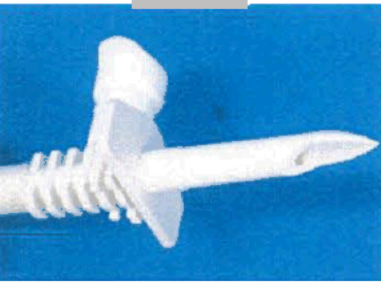
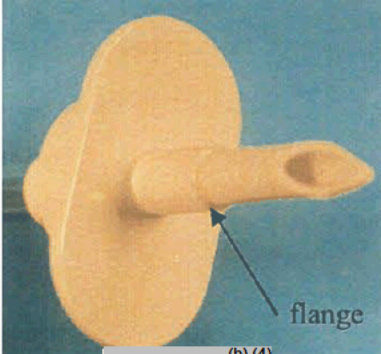
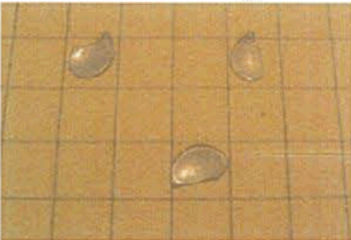
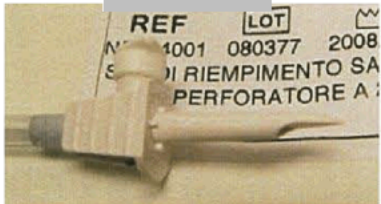
Baxter was asked to provide additional details regarding the information that prompted this advisory and the applicant responded to FDA in a letter dated August 09, 2013. Baxter noted the following in this correspondence:

Baxter Response: Baxter Canada received four complaints regarding generation of particulate matter upon spiking the ClinOleic bag with one compounding set and one administration sets. A full investigation is currently underway, however the initial investigation revealed that the particle found in each of these cases was the entire membrane disc from the twist off protector closure. Baxter is performing additional analysis on past Clinoleic complaints to determine if there are correlations to things such as spike geometry. A study is currently being designed to duplicate the TOP membrane separation such that we can better understand the exact parameters leading to a separated TOP. Understanding this is fundamental to gain confidence in any future recommendations that could reduce the possibility of TOP membrane separations. It is plausible that a spike with a sharp side tip, when rotated completely upon insertion and at the exact depth of the TOP membrane, could separate the membrane rather than just pierce the membrane. Based on this, leading parameters for this study are spike geometry (tip design, length, and width) and the technique/motion used when inserting the spike. The full investigation will be completed prior to Clinolipid launch in the US.

A Medical Risk Assessment was also conducted to review the situation and the risk was deemed to be low as 1.2 micron in-line filters are recommended by ASPEN/ESPEN and are typically used to administer lipids. Health Canada requested a Dear Healthcare Professional letter to remind clinicians to use a 1.2 micron filter when administering lipids to patients.

The Complaints from Europe include the following 4 observations in Spain (2), France (1) and Italy (1), (note that the date on the Special Report these figures were reproduced from has an “issue date” of May 21, 2012 but has author signature dates of August 2013):

Table 3. Observed fragments and spike implicated

Location of recovery of blue fragments	Fragments recovered (photo)	Spike used (type & photo)
Spain		(b) (4) parenteral nutrition bag” 
Spain		(b) (4) – Multilayer Parenteral (b) (4) 
France		“Baxa Exacta-mix TM non-DEHP”  flange (b) (4)
Italy		(b) (4)  REF LOT N° 4001 080377 2008 S DI RIEMPIMENTO SA PERFORATORE A :

Source: Reproduced from Applicant's submission

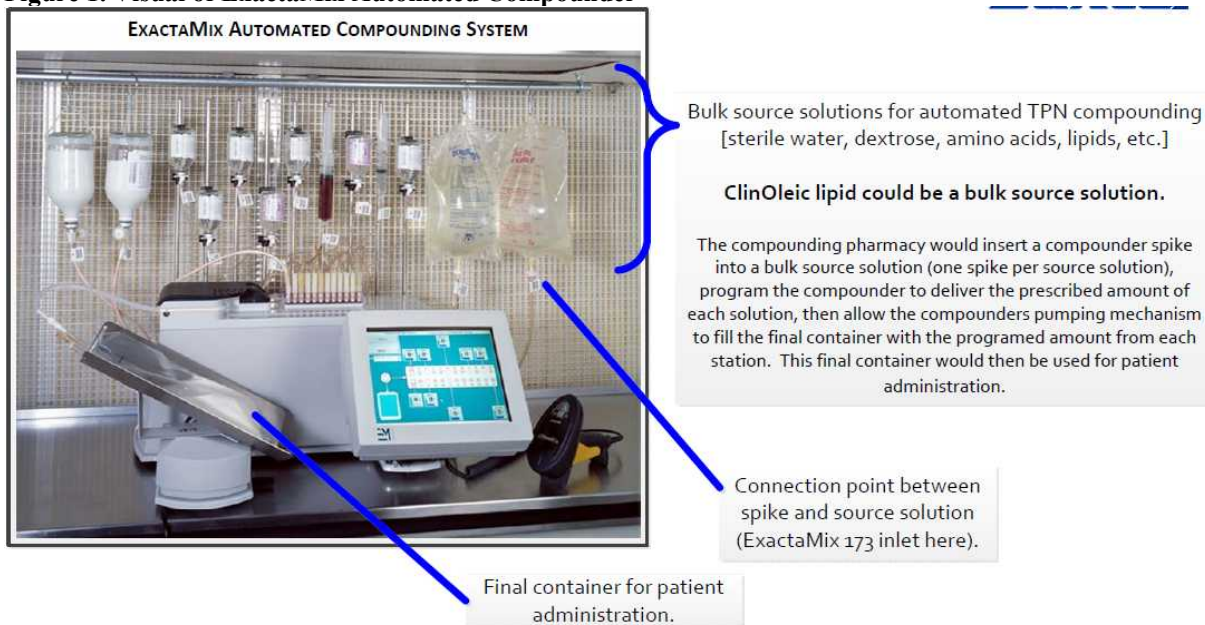
Baxter submitted the results of a medical risk assessment (MRA) to address the hazard of particulate matter being introduced into the TPN admixture. Baxter's conclusion was that "the resulting overall clinical risk is evaluated to be low."

The description of the issue and "how it was discovered" section describes it as such:

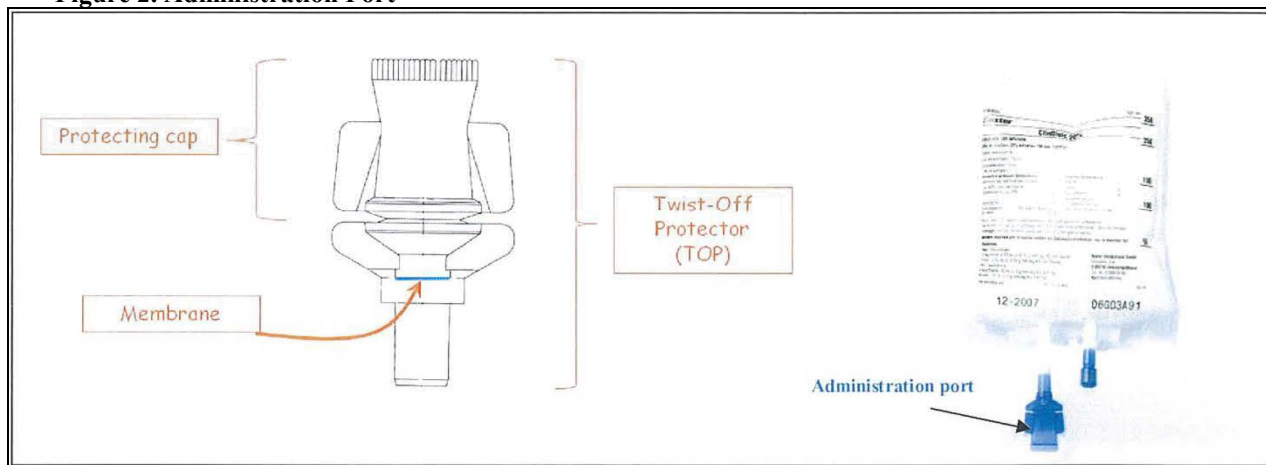
"Baxter Canada received two (2) complaints from two (2) different customers for Blue Particulate Matter (PM) floating inside Clinoleic 20% [...] after spiking with INLET, EXACTAMIX NON-VENTED HIGH VOLUME (Order Ref #173-manufactured by Baxter Englewood). In both cases the PM was discovered while preparing the unit for TPN or during TPN processing while using the ExactaMix Compounder. The blue particle was identified as the entire membrane disc from within the Twist off Protector (TOP) closure."

Note that the INLET listed is a specific type of spike, the ExactaMix 173 inlet, which connects the Clinolipid bag via plastic tubing to the Compounder (an automated pumping system that compounds multiple sterile ingredients into a finished solution in a single patient bag). Baxter provided the following visual (Figure 1), showing where the ExactaMix 173 inlet is placed in relation to the compounder set-up:

Figure 1. Visual of ExactaMix Automated Compounder



The administration port of the Clinolipid Bag, with the Twist-Off Protector and membrane (to be pierced by spike and the potential source of fragments) is shown in the diagram below:

Figure 2. Administration Port

As per the applicant's correspondence, the protecting cap is removed by the user, and then the spike is inserted through the membrane allowing flow of solution.

The applicant completed additional studies to evaluate other spike geometries in 2012 when the investigation of received complaint samples was performed.

As per the medical risk assessment (MRA) discussed above, the Baxter "confirmed that spike #173 should not be used with Clinoleic since the spike has a sharp point on the outer edge and when rotated fully could dislodge the entire membrane."

In addition, Baxter describes the risk of using this spike (#173) with the Clinolipid as thusly:

"Based on study 759-M-NIV [investigation of dislodgment event in France (see Table 3)] the estimated defect rate of the membrane being dislodged is 1-2% or a PODME rating [Probability Of Defect, Malfunction, or Error in use] of FREQUENT [Extremely likely; will occur frequently, >1:1000] when compounding using the BAXA product code [spike] 173."

An Information Request letter sent to the applicant on August 09, 2013 requested additional information and Baxter replied as such (emphasis added):

- Baxter plans a U.S. verification study, "to provide assurance on the acceptable interaction of various spikes in the U.S. and North America with the Clinolipid TOP. This **study, 64965**, will be completed before the ^{(b) (4)} Clinolipid production for the U.S. launch."
- Olimel, Oliclinomel, and Numeta are three other products that use the same Clarity system with the same Administration closure port called "Twist-Off Protector" (TOP). These are Triple Chamber Container versions of the Clinoleic bag and are sold outside of the United States.
- The Clarity Dual Chamber Container system used for Clinimix, marketed in the United States and globally, uses a different TOP material.

The stated purpose of Study 64965 was the following:

The purpose of this study is to verify the functional compatibility of a defined list of U.S Spikes with the (b) (4) administration site (Twist off protector closure) as represented by the Lipid 1 L (b) (4) (Clinoleic 20%). The system requirements that will be verified through this protocol will be the following:

For Direct Administration and Dispensing (b) (4) products:

- No leak (a detached droplet) during insertion
- No sliding out of the spike after (b) (4) submitted to a force of (b) (4) (Retention test).
- No sliding out/withdrawal of the spike after (b) (4) hanging.
- No leak (a consistent stream of bubbles) when internal pressure of (b) (4) is applied for (b) (4)
- Insertion force shall be equal or lower than (b) (4)
- Removal force shall be equal or greater than (b) (4)
- Fragmentation: spike insertion in 50 units (one insertion per unit) shall not generate more than 5 visible fragments (diameter equal or greater than (b) (4)) in total after the solution has been filtered on a (b) (4) pore size membrane.

For Gravity and Automated compounding products:

- No leak (a detached droplet) during insertion
- No fall out (withdrawal) of the spike, no leak (dripping fluid) at the spike-administration site junction and no visible fragmentation (diameter equal or greater than (b) (4)).
- Insertion force shall be equal or lower than (b) (4)
- Removal force shall be equal or greater than (b) (4)

CDRH provided a brief review of the preliminary results of Study 64965 in a review dated 09/30/2013. Jason To, the CDRH reviewer, noted that the applicant stated that Study 64965 was a functional test rather than a usability study, and acknowledges that the observations and failures that were documented in the study need to be further addressed. The applicant also stated that in order to make spike interface recommendations, further assessment of this study will take place in the form of an "Interface Evaluation and Recommendation Report." This report was not expected to be received until 2-3 weeks after the NDA goal date. CDRH provided a list of 4 questions to better understand the observations from this study (including leaks, acceptance criteria for spike removal and what spikes did not meet criteria for use with (b) (4) administration ports. The applicant provided brief responses where possible but ultimately referred to the final study report to be submitted after the goal date (i.e., the Interface Evaluation and Recommendation Report).

The Human Factors group at CDRH was also consulted to review the protocol of Study 64965 and on the data generated from this study. The results of Study 64965 were obtained very late in the review cycle (September 26, 2013) but were reviewed by CDRH Human Factors team.

QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, provided a consult review dated September 27, 2013 that reviewed Study 64965 from a Human Factors standpoint and provided recommendations. As noted in their review, the study report included specific values of force generated during insertion; however, "there was no analysis of how these

forces are correlated to forces that a user may generate that may result in particles generation and membrane dislodgement.” The reviewer also noted that although they believed that labeling should be used to help assure that in-line filter use is mandatory in hospitals/ institutions (i.e., providing precautions and statements about using appropriate filters and spikes), they remained concerned that the TOP membrane could embolize should a filter not be in place during administration. Therefore, the Human Factors review recommended a postmarket study to ensure that users understand the need for an in-line filter, choose the appropriate spike, and properly set-up and administer Clinolipid. At the time of finalization of this review, the wording for this post-marketing study was being discussed.

Discussions of Risk of the TOP Dislodgement with Applicant

A teleconference was held with Baxter on August 29, 2013 to discuss the applicant’s plans following identification of the TOP dislodgement issue. I note the following discussion points from the meeting minutes:

- Baxter states they are uncertain of how many units of the product and what percentage will be subjected to the procedure suspected of being responsible for the membrane detachment, although they are aware there are more compounding machines in the US than in Canada.
- Baxter says the complaints are “higher” with the Exactamix 173 spike and will be recommending the use of qualified spike to their compounding users.
- FDA expresses concern over the uniqueness of the Exactamix 173 spike. Baxter states the geometry (shoulder and spike length) is the main cause.
- FDA requests information with regard to other spikes that may interface with the Clinolipid product. Baxter states that the compound machine uses a specific spike. Baxter clarifies that the Exactamix 173 is ONLY for use in compounding machine, not in patient care sets.
- Baxter stated they are planning to test the majority of spikes available in U.S. market.
- Baxter stated they could provide a recommended technique for each spike, i.e., “if a product is longer than others, they could specify that less twisting would be needed.”
- FDA asked if eliminating the twisting motion could eliminate the issue: Baxter states that could be possible solution in addition to other compounding factors.
- Baxter states the detectability of the detachment membrane is “high” due to the color contrast of the foreign body, bag, and color of lipid as well as the size and floatation of the foreign body. Typical infusion line is smaller than the size of the foreign body so it is unlikely that it would go through the line. However, the material is softer and could fold up and enter the line.
- Baxter states that home users experience a more common practice to use in-line filters because the administration sets are included with the TPN before sent to the patient. Baxter clarifies that the administration set has a filter already attached so there is no further action required by the patient.
- Baxter states that the home care use is low compared to hospital use. Baxter states that home care use is (b) (4) units which is approximately (b) (4) of the total lipid market.
- Baxter states that all the reports of malfunction were coming from the pharmacy setting.

Extractables / Leachables

The safety of the CLARITY Container Closure System has been evaluated through tests, including an extractables/leachables characterization and its associated toxicological assessment and completion of USP Biological Reactivity and Physicochemical tests.

At the same time, during the review of the DMF (b) (4) for Clarity Container system, the concern on the extractables was discussed with the toxicology group on the potential extractable compounds using Pentane as a most suitable solvent for lipid product. Based on this discussion, a teleconference was conducted to convey needed information on the extractables, and the applicant has provided the final reports on extractables via email on June 11, 2013. The submitted data and report are deemed adequate (See non-clinical review by Sushanta Chakder and Dinesh Gautum).

Elemental Impurities

As noted in the CMC review, the product needs to include tests for elemental impurities per USP <232> limits. This was conveyed to the applicant during a teleconference on March 18, 2013. However, on May 24, 2013, the USP Council of Experts withdrew the General Notices USP <232>.

CMC review states that the drug product specification needs to be revised in conformance to draft ICH Q3D guidance for the “Elemental Impurities” in large volume parenteral drug product. This was communicated to the applicant during a teleconference dated June 4, 2013.

However ICH guidance does not set limits for (b) (4). Therefore, the applicant has proposed to follow the EMEA guidance to set limits for (b) (4) (and the ICH guidance for the other elements). Baxter has committed to submit specifications for elemental impurities as a CBE submission to the NDA after approval of the application as well as to commit to not launch their product prior to approval of this supplement.

The CMC reviewer considered the analytical procedure validated for the determination of aluminum in Clinolipid 20% lipid emulsion.

Phytosterol limits

FDA requested to add testing and limits for phytosterol content to the drug product specification. The applicant submitted an amendment (SN 011) dated June 7, 2013 proposing post-approval commitments. CMC found this proposal to be acceptable.

Although not evaluated as part of the CMC review, I note that the (comparative) phytosterol content of Clinolipid (see header “ClinOleic,” last column in Table 4) has been published in the literature² and is presented in Table 4. One of the co-authors of the paper (Guy Dutot) appears to be an employee of Baxter S.A.S.

² Steroidal Compounds in Commercial Parenteral Lipid Emulsions. Zhidong Xu, Kevin A. Harvey, Thomas Pavlina, et al. *Nutrients* 2012, 4, 904-921.

Table 4. Sterol composition of parenteral lipid emulsions ($\mu\text{g/mL} \pm \text{SD}$) *

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Source: Steroidal Compounds in Commercial Parenteral Lipid Emulsions. Zhidong Xu, Kevin A. Harvey, Thomas Pavlina, et al. *Nutrients* 2012, 4, 904-921.

On 02/11/2013 the applicant submitted the results of a literature report that reviewed the pathophysiology of parenteral nutrition-associated liver disease (PNALD) and the relationship between phytosterols and PNALD. Within this article the applicant presented the data shown in Table 5 regarding the phytosterol content of Clinolipid vs. Intralipid.

Table 5. Content of Phytosterols in Clinolipid and Intralipid

	Intralipid	ClinOleic
Manufacturer	Fresenius Kabi	Baxter Healthcare Corporation
Lipid components	soybean oil	olive oil/ soybean oil
Phytosterol Concentration (µg/mL)		
Publication: Xu et al, 2012 ^[90]		
Copyright Material Withheld		
Publication: Forchielli et al, 2010 ^[91] c		
Copyright Material Withheld		
Publication: Ellegard et al, 2005 ^[88]		
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,^[90] Table 4; Forchielli, 2010,^[91] Table 4; and Ellegard 2005,^[88] Table 2.

Source: Applicant, Review of PNALD Publications, submitted 02/11/2013, Table 3, page 55/67

Product Quality Microbiology

A product quality microbiology review was signed June 11, 2013 with a recommendation for approval from a quality microbiology perspective. No quality microbiology deficiencies were identified based on the information provided.

The DMF for the Clarity Container Closure System (DMF (b) (4)) was reviewed by quality microbiology and deemed adequate in support of this subject NDA. (b) (4)

The CMC reviewer also states that the sponsor commits to place the first three production batches on long term stability and thereafter, a minimum of one batch annually. The reviewer

concluded that the stability program is acceptable and the microbiological testing time points are appropriate.

CDRH Device Review Issues

Jason To, a biomedical Engineer in the Office of Device Evaluation in CDRH, submitted three consult reviews evaluating the bag (container closure system) for Clinolipid. These reviews are dated 03/05/2012[2013, date error], 06/10/2013, & 07/31/2013 and were administratively entered by Matt Brancazio (Regulatory Project Manager) into DARRTS on 5/20/2013 & 08/01/2013. Note that the additional (brief) review of the preliminary results of Study 64965 in a CDRH review dated 09/30/2013 have been discussed previously for the spiking issue that is not directly related to the evaluations described below.

An overview of each of these three reviews of the container closure system is provided below by review date.

March 05, 2012[sic, 2013 actual] (DARRTS: 05/20/2013)

- The functional tests performed on the injection site of the device were conducted per USP monograph <381>: penetrability, fragmentation, and self-sealing capacity. However, it appears that this standard has not been reviewed and recognized. Therefore, it is unclear as to whether or not the sponsor has adequately addressed concerns regarding the safety and effectiveness of the device. Furthermore, the sponsor has provided that all testing resulted in a “pass” evaluation. It is unclear as to what procedures, conditions, and parameters the sponsor has utilized in order to perform these tests.
- Deficiencies were conveyed to the sponsor to address the CDRH reviewer’s concerns

June 10, 2013 (DARRTS: 06/10/2013)

Baxter provided a response to deficiencies requested by FDA.

- “Based on the review of the information provided by the sponsor, Baxter has provided adequate testing methods and results per ISO 15747 Annex A, relative to CDRH’s concerns. However, the sponsor has stated that testing per “A.3 Resistance to Temperature Stability, Pressure, and Leakage” will be completed in 4 weeks, approximately by the end of June 2013. This information will be needed in order for CDRH to complete the device’s performance review. The sponsor will need to provide the methods and results of this testing to demonstrate that the device can meet its intended use specifications. Review of this device per ISO 15747 A.3 will be postponed until the sponsor provides this information.”

July 31, 2013 (DARRTS: 08/01/2013)

Baxter provided testing per ISO 15747 Annex A: A.3 Resistance to Temperature Stability, Pressure, and Leakage in Final Report 2708-RF-ERD, A (Addendum E.16).

- According to the reviewer, based on the review of the information provided by the sponsor, Baxter has provided adequate testing methods and results and the proposed device appears to be acceptable with respect to device performance testing.

4. Nonclinical Pharmacology / Toxicology

The applicant provided pharmacology, pharmacokinetics and toxicology studies of Clinolipid in rodents and nonrodents. The toxicity profile of Clinolipid was assessed in single-dose toxicity studies in mice and rats, and in repeat-dose toxicity studies for up to 3-months in rats and dogs. The toxicity profile of Clinolipid was compared with several soybean based lipid emulsions (Intralipid®, Ivelip® and Endolipide®).

The nonclinical reviewer notes that Clinolipid was well-tolerated and the toxicity profiles were comparable to the other lipid emulsions when administered intravenously to dogs and rats:

“In conclusion, the findings of the submitted nonclinical studies indicated that overall, the toxicity profile of ClinOleic was better or comparable to that of its comparators containing soybean oil only (Intralipid®, Ivelip® or Endolipide®). In repeated dose toxicity studies in rats and dogs of up to 90 days, ClinOleic showed no overt clinical findings and serious toxicity and was comparable to or better than other soybean-based lipid emulsions.”

General Nonclinical Pharmacology/Toxicology Considerations

Sodium oleate

The nonclinical reviewer asserts that sodium oleate is a novel excipient in Clinolipid 20%. This contrasts with the CMC reviewer's assertion that sodium oleate is a novel excipient, as the sodium oleate is the sodium salt of oleic acid, which is already a component fatty acid within Clinolipid. Regardless, the nonclinical reviewer concludes that Sodium oleate is not mutagenic, genotoxic or carcinogenic, and is not a reproductive or developmental toxicant. In a 24-week oral toxicity study in rats, no adverse effects were observed at doses up to 7,500 mg/kg/day. Thus, he concluded that there are no safety concerns for the amount of sodium oleate present in Clinolipid.

From a nonclinical standpoint, the nonclinical reviewer recommended approval of the NDA application. However he recommended revisions to the label to reflect the adverse findings in animals (rats and dogs) and doses at which these effects were observed.

(b) (4)

Elemental Impurities

The review team requested the applicant to determine the levels of the following elemental impurities (b) (4) from the finished drug product: (b) (4), and any other (b) (4) in the finished drug product.

The nonclinical reviewer included an applicant's table that presents the amount of different elemental impurities detected in Clinolipid. The anticipated human daily exposure (HDE, ug/day) to each of the elemental impurities were calculated based on a maximum daily dose of 625 mL for a 50 kg body weight. The proposed maximum daily dose appears to be based on the maximum dose *in adults* of 2.5g/kg/day and that Clinolipid contains 0.2g/mL lipids (i.e., 50kg x 2.5g/kg/day x 1mL/0.2g = 625mL/day)

Permissible daily exposures (PDEs) proposed in the ICH Q3D draft is shown in column 6 of Table 6.

Table 6. Elemental impurities in Clinolipid: Applicant's risk assessment

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

QL = Quantitation limit for the standards prepared on the day of analysis.

HDE = Human Daily Exposure

PDE = Permissible Daily Exposure. Reference 2.

¹ Testing was performed on three units from each of the 3 respective primary stability batches manufactured in support of NDA 204508. Reference 8. No values were observed above the QL.

² Calculated as [(QL (ng/mL) x 625 mL/day) / (1000 ng/µg)]

Source: Reproduced from nonclinical review, page 10.

The nonclinical reviewer concluded that the (b) (4) impurities in Clinolipid are several-fold lower than the PDEs proposed in the ICH Q3D draft.

In addition the nonclinical reviewer states, “Since (b) (4) are not listed in the ICH Q3D draft guidance, the current EMEA guidance was consulted for their PDEs. According to EMEA guidance, (b) (4) are also several folds lower than the PDE values. Thus, the levels of these (b) (4) impurities are within acceptable limits and there are no safety concerns.”

Extractables / Leachables (from container closure system)

Safety evaluation of extractables

As per the nonclinical review, the components of the container closure system have been evaluated for appropriate compendial biomaterials testing as per international standards organization (ISO) and/or the United States Pharmacopeia (USP) as summarized below. All components passed the recommended compendial tests.

Safety evaluation of the leachables

The applicant identified leachables under simulated conditions. According to their study report, an accumulation level of leachables identified in Study 7 (Table 7) is appropriate for Clinolipid 20%. In this study, 100 mL lipid was filled in the container, autoclaved and stored for 24 months, and the targeted leachables were determined.



Source: Nonclinical review, page 95

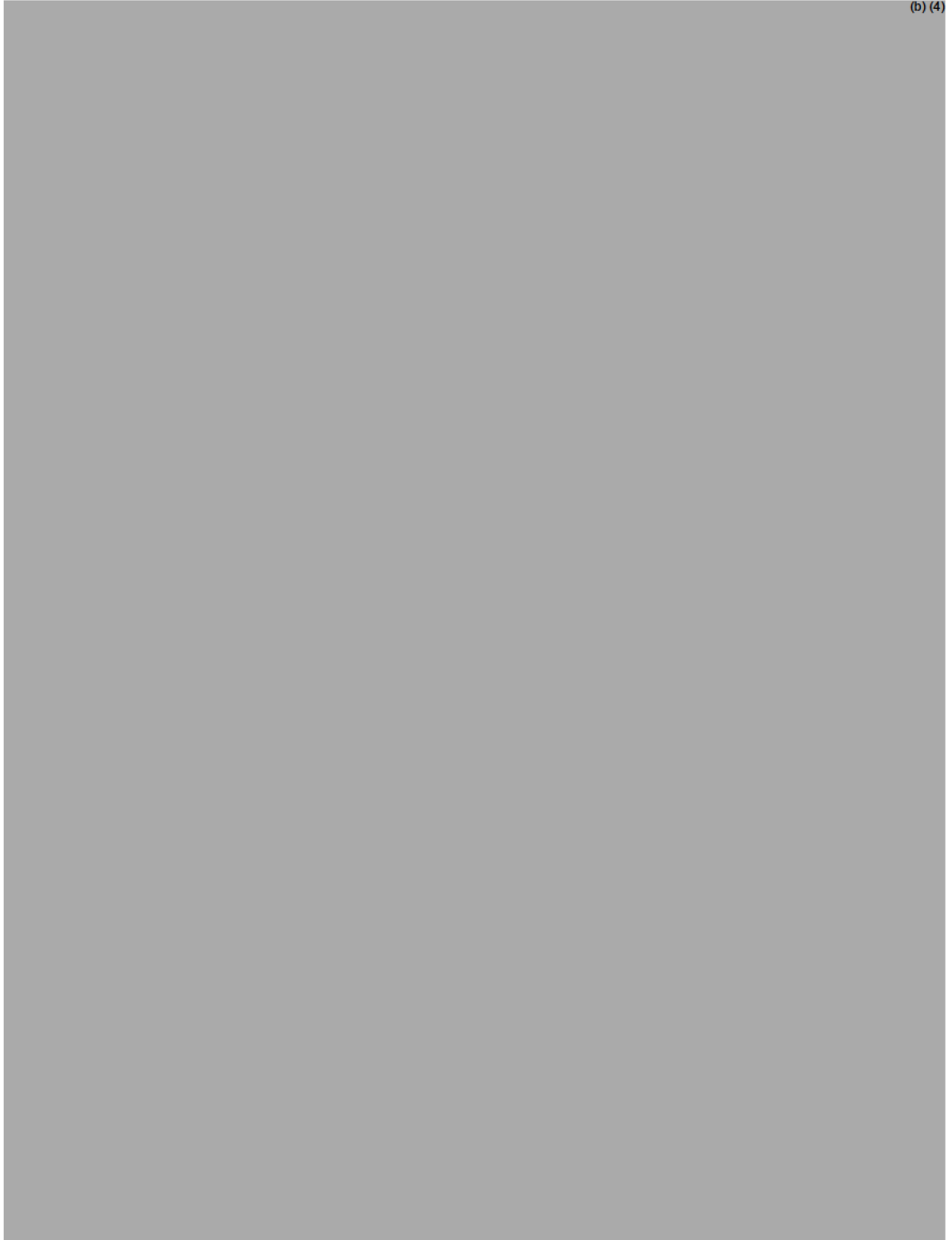
Safety evaluations of individual leachable were performed based on the recommended daily dose of Clinolipid 20%. The originally proposed

[REDACTED]

[REDACTED]

PDE (Permitted Daily Exposures) were calculated by the nonclinical reviewer based on a formula similar to that used in the ICH guidance [REDACTED]. The PDE was adjusted by variability between species, individuals, length of exposure in toxicity studies, severity of toxicity observed, whether NOEL was observed and a safety factor.

The nonclinical reviewer performed detailed assessments for each of the leachables identified below and concluded that all potential extractables and leachables from the Clinolipid 20% container closure system are within the recommended safety limit and appear to be acceptable. The following molecules and the nonclinical conclusions are reproduced below:



Pharmacology/Toxicology and Pharmacokinetic Studies

As per the nonclinical review (Section 1.1 of review), the applicant has performed six pharmacodynamic (PD) studies in rats, one PD study in dogs and one PD *in vitro* study with rabbit RBCs.

In vivo and *in vitro* studies Pharmacokinetic (PK) studies were also performed in mice, rats (or rat plasma), and dogs.

From the nonclinical review (Section 1.1, page 13), it appears that the applicant performed (and nonclinical reviewed) two single-dose toxicity studies (one in mice and one in rats), eleven repeat dose toxicity studies in rats, rabbits and dogs (range 14 to 91 days), one local tolerance study in rats, one *in vitro* study to determine effects on human peripheral white blood cells and one *in vivo* study to determine effects on rat spleen lymphocytes.

I have attempted to summarize the following key conclusions from the nonclinical reviewer:

- Clinolipid was able to maintain similar levels of essential fatty acids (EFA) compared to Intralipid when infused to rats, while Clinolipid contributed three times less saturated fat compared to Intralipid.
- The mean H50 (time to hemolyze 50% of RBCs) of rabbit RBCs for Clinolipid was significantly longer (5.22 h) than that of Intralipid (3.45 h)
- Higher levels of Vitamin E (in the form of α -tocopherol) in Clinolipid compared to soy-oil based IV lipid emulsion did not afford any additional protection against pro-oxidant shock in rats.
- Clinolipid modulates biliary secretion with reduced biliary phospholipids and cholesterol more than that with Intralipid.
- Rats that received a total parenteral nutrition as Clinolipid had higher bile output than the soy oil based comparators groups. Rats that received lipid emulsions containing egg phospholipid with a low phosphatidylcholine/phosphatidylethanolamine (PC/PE) ratio (i.e., Intralipid) showed significantly reduced biliary flow relative to lipid emulsions containing phospholipid with a high PC/PE ratio (including Clinolipid).
- The administration of 5 mL of Clinolipid over 30 sec had no observable hypotensive effect in cats.
- *In vitro* studies in rat plasma suggest Clinolipid may undergo lipolysis faster than Intralipid.
- *In vitro* study suggested that Apo A-I binding was greater for the lipid particles from soybean oil (Intralipid®, Ivelip®) than the emulsions containing soybean and olive oil.
- In rats and dogs, both fat emulsions, Intralipid and Clinolipid, were cleared in a comparable fashion.

In toxicology studies in mice, the main organs of toxicity were the kidney, spleen and liver. Gross observations in rats that were necropsied at the end of toxicology studies included lesions in the liver, kidney, lungs and spleen. As noted by the nonclinical reviewer, the major signs of toxicity were: slight hemolytic anemia, transitory thrombocytopenia,

hypercholesterolemia and hepatic pathology of lipid and pigmentary overload. At a dose of 15 mL/kg/day in dogs, only very slight lipid and pigmentary overload of the liver were noticed. In rats, the dose of 30 mL/kg/day was well tolerated but in the dogs, the same dose was associated with adverse effects (pigmentation and vacuolation in the liver). The nonclinical reviewer states that the dose of 15 mL/kg/day may be considered the highest dose without significant adverse events in dogs.

Special Toxicology Studies

A study in rats was performed to evaluate the effects of Clinolipid when administered extravascularly (SC or intradermal) by accident. The nonclinical reviewer noted that tissue necrosis did not occur following subcutaneous or intradermal administration of Clinolipid, and absorption from the injection sites was complete by 14 days after administration. Thus, he concluded that an accidental extravascular administration of Clinolipid may not have any serious side effects.

An *in vitro* study evaluating the stimulatory or inhibitory effects of Clinolipid on different immune functions (lymphocyte proliferation, T-cell activation markers expression, and cytokine release) was performed using peripheral white blood cells were collected from healthy volunteers. An *In vivo* study evaluating the effects of Olive oil based lipid emulsion on lymphocyte activation was also performed in rats.

Based on the results of these studies, the nonclinical reviewer stated that these findings suggest that an olive oil-based lipid emulsion could modulate immune response and thus reduce the inflammatory response and that olive oil may offer an immunologically neutral alternative to soybean oil for use in parenteral lipid emulsions. However, I consider these statements to be speculative in nature as the applicant has provided evidence that Clinolipid offers no advantages with respect to being less “pro-inflammatory” than other IV lipid emulsions.

Carcinogenicity

No carcinogenicity studies were submitted.

Reproductive toxicology

No reproductive and developmental toxicology studies were submitted.

5. Clinical Pharmacology / Biopharmaceutics

The results of four clinical pharmacology studies were submitted in support of this NDA; however, as noted by the clinical pharmacology reviewer, all four studies were considered to be exploratory and as a consequence, the information was of limited value and was not included in labeling. The reviewer also notes that these studies were conducted with 6-9

healthy male subjects each and date from 20-24 years ago. In addition, the bioanalytical methods were not described in detail and method validation results were not provided. As a result, much of the applicant's proposed labeling language for Section 12 Clinical Pharmacology, of the label, was deleted. See the clinical pharmacology review for details.

The clinical pharmacology reviewer commented on each of the four studies, most notably their limitations (including analytical methods). It does not appear that the reviewer drew any substantial conclusions from the studies. However, she did acknowledge that "...it seems reasonable to accept an equivalent contribution of calories between the two lipid emulsions [Clinolipid and Intralipid] for the purposes of parenteral nutrition..." (based on Study Number C-88-CSW-6/3-04-F).

Olive and soybean oils have a natural content of Vitamin K that may counteract the anticoagulant activity of coumarin derivatives, including warfarin. The clinical pharmacology reviewer concurred with the applicant's proposed inclusion of this interaction within the label.

6. Clinical / Statistical - Efficacy

As noted by the clinical reviewer, Dr. Klaus Gottlieb, the applicant provided the results of 31 studies and clinical trials. A complete listing is in the Appendix of the clinical review. 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 three treated patients, reducing the effective number of relevant studies for the efficacy analysis to two.

It should be noted that a formal statistics review was not performed by FDA staff for any of these studies. The abbreviated statistical review by Behrang Vali commented that they considered this application to be NAI in their filing review (signed 02/05/2013):

"No individual clinical study submitted appears to be identifiable as pivotal for efficacy review and labeling purposes. The submitted study results should be considered descriptive or observational only as they do not rely on appropriate inferential statistics or trial designs that would be considered adequate to support specific endpoint testing. At the time of filing, we considered this application as 'No Action Indicated'."

Tabulation of the completed controlled studies comparing Clinolipid to Intralipid in adult and pediatric patients is presented in Table 8 & Table 9.

Table 8. Completed Controlled Studies Comparing Clinolipid to Intralipid in Adult Patients

Study ID	Objective	Design	Treatments	Number Of Subjects	Patient population	Duration
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	20 planned 7 treated 4 ClinOleic, 3 Intralipid	ICU patients following abdominal surgery	5 days
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	20 planned 27 treated 15 ClinOleic, 12 Intralipid	ICU patients following gastrointestinal surgery or multiple trauma	5 days
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	16 planned 20 treated 11 ClinOleic, 9 Intralipid	ICU patients following gastrointestinal surgery or multiple trauma	5 days
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	20 planned 20 treated 11 ClinOleic, 9 Intralipid	ICU patients following gastrointestinal or vascular surgery, multiple trauma or burns	5 days
C 89 CSW 6/3 08 F*	Evaluate efficacy and safety with prolonged use (≥ 15 days)	Multicenter, randomized, open label, active control	ClinOleic versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day)	48 planned 48 treated 24 ClinOleic, 24 Intralipid	Hospital patients requiring total parenteral nutrition	15 days to 6 months
C 89 CSW 6/3 10 F*	Evaluate safety with long-term use (≥ 26 days)	Multicenter, randomized, open label, active control	ClinOleic versus Intralipid adjusted to caloric need	50 planned 22 treated 12 ClinOleic, 10 Intralipid	Hospital or ambulatory patients requiring supplemental parenteral nutrition	26 days to 1 year
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)	12 planned 3 treated 2 ClinOleic, 1 Intralipid	Hospital patients requiring total parenteral nutrition	15 days to 6 months
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)	20 planned 24 treated 13 ClinOleic, 11 Intralipid	Hospital patients requiring total parenteral nutrition	5 days minimum
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	200 planned 200 treated 100 ClinOleic, 100 Intralipid	Hospital patients requiring parenteral nutrition for at least 50% of needs	5 days

*Study description proposed by review team for inclusion into labeling.

Source: Clinical Review, Section 5.1, page 22

Table 9. Completed Controlled Studies Comparing Clinolipid to Intralipid in Pediatric Patients

Study ID	Objective	Design	Treatments	Number Of Subjects	Patient population	Duration
C 88 CSW 6/3 03 F	Evaluate mediumterm tolerability and effect on erythrocyte and plasma fatty acid profiles	SC RDO L AC	Clinolipid versus Intralipid 2.5 g/kg/day	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
CT 2402/P14/ 93/F	Evaluate longterm efficacy and safety	SC RD DB AC	Clinolipid versus Intralipid adjusted to caloric need (maximum rate of 6.0 g/kg/day)	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)	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

Source: Clinical Review, Section 6.1.7, page 33/101

As discussed by the clinical reviewer, the applicant desires an indication for Clinolipid as “a source of calories and essential fatty acids” and the review team therefore focused the review of efficacy on those studies that provided the most robust evidence that Clinolipid can be approved with these claims.

Dr. Gottlieb notes that many of the submitted studies in this NDA were “chiefly conducted to evaluate biomarkers that would show a possible advantage of Clinolipid over other lipid products in the area of inflammation and immunity.”

As tabulated in Section 5.2 of his review, Dr. Gottlieb describes multiple clinical endpoints across the trials comparing Clinolipid against an active comparator. I note some of the following metrics that were obtained across these trials:

- Albumin
- Transthyretin (aka, “prealbumin”)
- Nitrogen balance
- Anthropometrics
- Essential fatty acid deficiency (via the Holman Index)
- Triglycerides
- Fatty acids
- Inflammation
- Oxidation

Across these trials, there was no evidence provided that Clinolipid provides any advantage over soybean-oil based IV lipid emulsions, including the metrics outlined above.

There was significant discussion among the clinical reviewers on the team on how to present the adult clinical data in Section 14 Clinical Studies, of the label. The sponsor had initially presented data obtained from 386 adult and 198 pediatric patients treated with Clinolipid 20% in 23 completed clinical efficacy and safety studies. However pooling so many trials seemed to be of limited value and that studies C89CSW6/308F and C89CSW6/310F (bolded in Table 8 above) were deemed sufficient to describe evidence that Clinolipid is comparable in respect to provision of energy as the approved soybean oil based IV lipid emulsion.

These two studies are described as “Study 1” and “Study 2” within the label (currently being negotiated with the applicant):

Study 1 was a randomized, open-label, multicenter study. Forty eight (48) patients, aged 17 to 75 years, requiring ≥ 15 days (mean 22 days) exclusive parenteral nutrition (TPN) were enrolled and randomized to either Clinolipid or a pure soybean oil based IV lipid emulsion. Nutritional efficacy was assessed by anthropometric indices (body weight, arm circumference, skin-fold thickness), biomarkers of protein metabolism (total protein, albumin) and lipid metabolism. Anthropometric criteria (body weight, arm circumference, and skin fold thickness) were comparable for both groups. Mean total serum protein and albumin increased similarly in both groups.

Study 2 was a randomized, open label multicenter study that enrolled 22 patients aged 32-81 years who required long-term parenteral nutrition. Twelve 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 had similar outcomes for weight, weight loss, mid-arm circumference and triceps skinfold thickness.

Clinolipid as a Source of Calories

Dr. Gottlieb asserts the following in his review with regards to establishing Clinolipid as a source of calories:

“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.”

It is known that the energy content of lipids is approximately 9 kcal/g. Since the components of Clinolipid are specified, the caloric content can be readily calculated. Table 10 presents the caloric content of Clinolipid 20%.

Table 10. Sources of energy (calories) in Clinolipid 20%

	ClinOleic	
Component	Mass Concentration (g/L)	Energy Concentration (kcal/L)
Oils	200	1800 ^a
Egg phospholipids	12	108 ^a
Glycerin	22.5	90 ^b
Sodium oleate	0.3	2.7 ^a
Total energy		2000.7

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

Source: Reproduced from clinical review, page 27

Although there should be no doubt regarding the caloric content of Clinolipid, the energy requirements for any given patient are variable. The applicant states the following in this regard in their originally proposed labeling:

(b) (4)

However, as per the ASPEN guidelines³, adult energy requirements range from 20–30 kcal/kg. In addition, the guidelines state that the standard distribution of non-protein calories should be 70–85% as carbohydrate and 15–30% as fat. The guidelines also state that this distribution may be adjusted based on tolerance and that “there is limited clinical benefit when fat content exceeds 30% of nonprotein calories.”

Based on these estimates, in adult patients it is recommended that the fat content of parenteral nutrition formulations not exceed 2.5 g/kg/day. (b) (4)

The applicant has therefore based their proposed dosing on the ASPEN guidelines, as noted in the *initial* labeling submitted to the NDA:

Adult Patients:

The maximum daily dose of ClinOleic 20% should be based on individual total nutritional requirements and patient tolerance. The usual dosage is 1 to 1.5 g/kg/day (equal to 5 to (b) (4) mL/kg/day). The daily dose should not exceed 2.5 g/kg/day. The initial infusion rate should not exceed 0.1 g (equal to 0.5 mL) per minute for the first 15 to 30 minutes. If (b) (4), (b) (4), then gradually increase until reaching the required rate after (b) (4).

³ Safe Practices for Parenteral Nutrition. Mirtallo J, Canada T, Johnson D, Kumpf V, Petersen C, Sacks G, Seres D, Guenter P; Task Force for the Revision of Safe Practices for Parenteral Nutrition. JPEN: J Parenter Enteral Nutr 2004 28: S39. PMID: 15568296

This proposed dosing regimen was consistent with the approved Intralipid 20% label. The proposed labeling also contains additional dosing and monitoring recommendation based on best clinical practice guidelines.

Proposed label Section 5.4 “Fat Overload Syndrome” in Warnings & Precautions of the label describes the potential for patients to have “a reduced or limited ability to metabolize the lipids contained in Clinolipid” that “may result in a syndrome characterized by a sudden deterioration in the patient's condition accompanied by fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, liver fatty infiltration (hepatomegaly), deteriorating liver function, and central nervous system manifestations (e.g., coma).” Fat overload syndrome is a well-described phenomenon in the literature and has been known to be associated with IV lipid emulsions. The syndrome is usually reversible when the infusion of the lipid emulsion is stopped.

Adequate Source of Essential Fatty Acids

As discussed in detail in the clinical review, only two fatty acids are considered to be essential to human health. They are both long chain (18-carbon) polyunsaturated fatty acids (PUFA) that cannot be synthesized by mammals, since mammals lack the requisite enzymes to insert a double bond at the n-3 and n-6 position of the fatty acid chain. 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.

Docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (ARA, 20:4n-6), metabolites of ALA and LA, respectively, are important structural components of the specialized membrane lipids of the human central nervous system and are therefore considered important EFAs for human neonates. 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 reversible with administration of EFA. However, as noted by Dr. Gottlieb in his review, “in the infant EFA deficiency may have more far-reaching and possibly permanent consequences for neurological development.”

EFA Content of Clinolipid

In the Integrated Summary of Efficacy (Section 4.3.3.2), the applicant describes the EFA content of Clinolipid thusly:

“ClinOleic is a lipid emulsion comprising a mixture of refined olive oil and refined soybean oil in an approximate ratio of 4:1 (olive:soy), corresponding to an essential fatty acid content of 20% of the total fatty acid content. The lipid is manufactured at a concentration of 20% (ie, 20 g/dL). Thus, the essential fatty acid content represents approximately 4 g/dL. ClinOleic contains approximately 18.5% linoleic acid and 0.2% arachidonic acid (total n-6 fatty acids approximately 18.7%, or 0.0374 g/mL). ClinOleic contains 2% alpha-linolenic acid and 0.12% DHA (total omega-3 fatty acids approximately 2.12%, or 0.0042 g/mL).”

In contrast to Clinolipid, the applicant notes that “commercially available soybean emulsion,” i.e., Intralipid, contains approximately 55-60% of total calories as linoleic acid (LA) and 3-4% of calories as ALA. This represents a substantially higher LA content than Clinolipid.

The applicant also presents guideline recommendations for the intake of linoleic acid (omega-6 fatty acid) and alpha-linolenic acid (omega-3 fatty acid), as well as published literature on diagnosing EFAD (based on the Holman Index or triene: tetraene ratio⁴).

As per the applicant, the recommendations for adult linoleic acid intake range from 1 to 4 percent of total energy intake (% E) and for alpha-linolenic acid (omega-3 fatty acid) from 0.2 to 0.5% E. The applicant admits, however, that “[t]he wide range of recommendations stems from the small amount of actual data on which to base the recommendations.⁵”

Based on the above estimates, the applicant provides the calculated amounts of Clinolipid that are required to supply adequate amounts of omega-6 and omega-3 EFA, respectively, to a 75 kg adult patient over the range of recommended essential fatty acid intakes. The estimates for omega-6 FA are presented in Table 11. (The adequacy of omega-3 EFA is not discussed further in my review as a deficiency syndrome for these FA has not been clearly described).

Table 11. Calculated Quantities of Clinolipid (ClinOleic) Required to Deliver Adequate Omega-6 Fatty Acids in Adults

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

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

The applicant presented the requirements for omega-6 polyunsaturated fatty acids (primarily

⁴ The Holman index (also referred to as the triene/tetraene ratio) is commonly used to diagnose EFAD. The index is calculated by dividing the level of eicosatrienoic acid (omega-9 fatty acid; Mead acid) by the level of arachidonic acid (omega-6 fatty acid). Inadequate supply of omega-6 EFA decreases levels of arachidonic acid, which is derived from the dietary EFA linoleic acid. The reduced inhibition of elongation of oleic acid to Mead acid by long-chain omega-6 or omega-3 fatty acids results in increased levels of Mead Acid. An index greater than 0.2 to 0.4 has historically been used as the cutoff suggestive of EFAD.

⁵ Integrated Summary of Efficacy, Section 4.3.3.1, page 190/767

linoleic acid) for

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

7. Safety

See Dr. Gottlieb's review for a detailed discussion of the safety findings of this application.

General Safety Considerations

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.

In comparative studies, patients received Clinolipid or a soybean oil-based lipid; in single-arm studies they received Clinolipid 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 Clinolipid, and 287 (adult, 248; pediatric, 39) patients received a soybean oil-based lipid. Dosing was individualized to the needs of individual patients.

As is evident from Dr. Gottlieb's review of safety, it is difficult (if not impossible) to distinguish whether observed adverse "events" were due to the underlying disease or condition, other interventions (surgical or device-related), concomitant treatments (including IV carbohydrates, amino acids or other parenteral fluids) or to the administration of Clinolipid itself.

For example, overall the three most common fatal serious adverse events in 386 adults who received Clinolipid was septic shock (1.3%), followed by subarachnoid hemorrhage (0.5%) and cardiac arrest (0.3%). In comparative studies, there was no convincing evidence that the safety profile of Clinolipid differed from Intralipid, including non-fatal SAEs.

In comparative trials, the clinical reviewer also could not discern any clinically meaningful differences between Clinolipid and Intralipid with respect to laboratory findings (hematology and chemistry) and vital signs.

Importantly, the data from a number of clinical studies indicate that Clinolipid and soybean oil based lipid emulsions have no differences with respect to any effects upon the immune/inflammatory and oxidative systems during infusion as part of parenteral nutrition in a large variety of pathological states.

The applicant performed subgroup safety analyses (ISS Section 7.2.1.6) on the following adult patient sub-types enrolled across studies:

- ICU -treated Injury or Surgery Patients (n=101)
- Medical/Surgical Patients (n=70)
- GI Surgery Patients (n=44)
- ICU-treated Burn Patients (n=22)
- Hemodialysis Patients (n=41)
- Intestinal Failure Home Care Patients (n=31)

There were no clinically meaningful differences between the safety profiles of Clinolipid vs. the comparator IV lipid formulation in these subgroups.

Product Quality Related Safety Issues

Other safety issues involving lipid injectable emulsions include potential for destabilization of the emulsions, the size of the fat globules (forming the emulsion) and the droplet size of the lipid emulsion during infusion. These issues, as well as stability, trace element and aluminum content, leachable/extractables from the container closure, etc., are covered within the CMC and Nonclinical reviews. Clinical data was not collected for Clinolipid in a manner that can be used to inform setting limits or controls on these complex set of issues. This is an evolving area of understanding.

Special Safety Concern: Phytosterols

Phytosterols are plant sterols that are poorly absorbed by the gut and compete with the absorption of cholesterol. In contrast to the intestinal route, where the absorption is purported to be 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).

Although PNALD was not observed in any of the studies submitted to support this NDA, this is not surprising given the relatively short duration of the trials and patient populations enrolled.

As noted by Dr. Gottlieb, the applicant concedes that the phytosterol content of the lipid emulsions provided as part of PN therapy is one factor associated with the development of PNALD. The applicant also notes that 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).

8. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application.

9. Pediatrics / Maternal Health

Consults were sent to both Pediatric and Maternal Health staff (PMHS). The PMHS reviewers participated in team meetings throughout the review.

The purpose of the first consult to the Pediatric Staff was to confirm PREA does not apply to this application, assist with labeling for both pediatric and maternal health and to assist with potential (non-PREA) PMRs in pediatric and neonatal patients. This NDA did not trigger PREA because Clinolipid was not considered to have a new active ingredient (relative to Intralipid).

In their September 09, 2013 consult, the pediatric reviewer discussed a previous PMHS consult (signed July 18, 2011) that was done under IND#7488, which contains a record of pre-NDA meetings DGIEP had with the sponsor (Baxter). In this 2011 consult memo the PMHS reviewer made the following recommendations:

(b) (4)



(b) (4)

(b) (4)

With regarding to extrapolation of efficacy, since the caloric content of Clinolipid is specified and is 100% bioavailable, there is no reason to believe that Clinolipid wouldn't be a source of calories in both adults and children. However, safety in the pediatric population would still need to be evaluated, particularly since the potential for off-label use is anticipated.

PMHS agreed with DGIEP's plan during the review to create postmarketing requirements (under FDAAA) or postmarketing commitments to obtain adequate pediatric data. In addition, the Pediatric Staff provided labeling language that was for the most part incorporated into the label prior to labeling negotiations began with the applicant. However, it should be noted that further discussion altered the language initially proposed by PMHS for inclusion into the label.

(b) (4), all pediatric information was summarized in Subsection 8.4, which reference to other appropriate sections as needed. PMHS also recommended a Limitation of Use section indicating that Clinolipid is not recommended for use in pediatric patients.

The DGIEP review team also asked for help reviewing the proposed labeling for Pregnancy and Nursing Mothers and to provide any insight into potential risk of inadequate essential fatty acid intake during pregnancy. There was concern that pregnant women may have a need for parenteral nutrition due to severe hyperemesis gravidarum or other serious medical or surgical conditions where oral or enteral nutrition are not possible. Leyla Sahin, a medical officer in PMHS, provided a separate Maternal Health Team consult review addressing these issues (dated September 10, 2013.)

The Maternal Health staff reviewer, recommended that "the relevant section of Clinolipid labeling state clearly that the linoleic acid content is lower than the reference product; however, additional statements in the Pregnancy section of labeling are not warranted." However ultimately it was felt by the review team that language should be inserted into the label that the ability of Clinolipid to provide adequate amounts of EFA to the developing fetus remains unknown.

The Maternal Health staff reviewer also recommended revisions to Section 8.1 Pregnancy and Section 8.3 Nursing Mothers. These include adding the following statement to 8.1:

There are no adequate and/or well-controlled studies with ClinOlipid 20% in pregnant women.

The PMHS reviewer notes that in accordance with the Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008, when only animal data are available, just the

presence or absence of drug in milk is noted and presented in the labeling, not the amount. Therefore PMHS recommended the following edits to Section 8.3:

It is not known whether Clinolipid (b) (4) is present (b) (4) in human milk. Because many drugs are (b) (4) present in human milk, caution should be exercised when ClinOlipid (b) (4) is administered to a nursing woman.

10. Other Relevant Regulatory Issues

OSI Inspections

The Office of Scientific Investigations was not consulted and did not perform inspections of clinical sites, primarily due to the historical nature of the clinical studies conducted.

Special Government Employees

Two Special Government Employees (SGEs) were cleared during the review of this application to provide expert advice on two topics:

- **Richard E. Ostlund, M.D.**, Director, Core Laboratory for Clinical Studies, Division of Endocrinology, Diabetes and Lipid Research, Washington University School of Medicine

Dr. Ostlund was identified as a leading expert in nutrition with extensive experience with lipid and cholesterol physiology as well as commercial manufacturing. He provided his expertise in evaluating the 02/11/2013 submission of the application entitled, "Review of PNALD Publications." He was specifically tasked with providing his thoughts on how to clinically evaluate the effects of intravenously administered phytosterols and well as the feasibility of manufacturing a phytosterol-deficient oil for purposes of clinical investigation. The result of his work, appended to the end of Dr. Gottlieb's clinical review, encouraged the review team to engage the applicant to further evaluate the role of phytosterols in PNALD.

- **Timothy O. Lipman, M.D.**, Emeritus Chief, GI-Hepatology-Nutrition Section, Department of Veterans Affairs Medical Center

Dr. Lipman was identified as having substantial experience in the care of patients receiving parenteral nutrition and as a published author, to have an understanding of the literature surrounding parenteral nutrition. His role in review of this application has been ongoing. He has provided the review team his thoughts on how to evaluate clinically meaningful outcomes in various patient populations receiving IV lipid emulsions.

11. Labeling

Proprietary name

The previously proposed proprietary name, (b) (4), was found to be misleading by DMEPA (b) (4)

This preliminary finding was communicated to the Applicant on March 7, 2013. As a result, the Applicant withdrew the name, (b) (4), and submitted the alternative proprietary name, Clinolipid, on March 26, 2013.

DMEPA found the proposed name, Clinolipid, acceptable in a Proprietary Name Review dated June 20, 2013. The re-evaluation of the proposed proprietary name, Clinolipid, (review dated 09/06/2013) did not identify any vulnerabilities that would result in medication errors with any additional names noted in this review. Thus, DMEPA has no objection to the proprietary name, Clinolipid.

Labeling

DMEPA submitted a review (dated 7/12/2013) that evaluated the proposed container, carton and insert labeling for Clinolipid for areas of vulnerability that could lead to medication errors. They recommended a “dual expression” of strength for this drug product in % (20%) and grams/mL and recommendations for The Mixing and Limitations section (under Dosage and Administration) to be reorganized to improve retrieval of information.

Note that DMEPA’s Section 2 Mixing Guidelines recommendations (Appendix F of their review) differ from the current label since that section of the label was extensively revised and re-ordered. Nevertheless, the key items of DMEPA’s recommendations have been incorporated into the label.

See recommendations for labeling revisions described in each review discipline section, where applicable. The team made the following notable revisions to the Physician’s Labeling originally submitted by the applicant (label negotiations were ongoing at the time of finalization of this review):

Boxed Warning

Edited sponsor’s proposed language to align with having an adult only indication.

Indications and Usage

A limitation of use statement was added to indicate that the safety and effectiveness have not been established in pediatric patients. Also that the omega-3: omega-6 fatty acid ratio in Clinolipid has not been shown to improve clinical outcomes compared to other intravenous lipid emulsions.

Dosage and Administration

The applicant originally relied on the Intralipid label to inform the layout of this section, however extensive reordering and revisions were made on the placement of information. DMEPA recommendations were incorporated.

A new section, 2.1 Use of an Inline Filter, was added to make the use of an in-line filter more prominent in this section. This was important given the issues with dislodgement of fragments from the administration port noted in foreign safety reports.

Also Section 2.3 contains language not use the EXACTAMIX Inlet H938173 with an EXACTAMIX compounder to transfer CLINOLIPID injection. This inlet spike has been associated with dislodgement of the administration port membrane into the CLINOLIPID injection bag.

Contraindications

Revised as such:

- Known hypersensitivity to egg or soybean proteins or to any of the ingredients, including excipients.
- Severe hyperlipidemia (serum triglyceride concentrations above 1000 mg/dL) or severe disorders of lipid metabolism characterized by hypertriglyceridemia.

Warnings & Precautions

Note that section 5.6 was extensively revised to provide monitoring instructions for EFAD. A new section was added, 5.9 Risk of Parenteral Nutrition Associated Liver Disease. Section 5.10 Hypertriglyceridemia was also added to the proposed label and also includes the reference for the Contraindication.

Adverse Reactions

A generally descriptive approach was taken to describe the safety data given the multiple studies submitted to the safety database.

Use in Specific Populations

Pediatric information was revised and included based on discussions with PMHS staff noted in this review.

Description

Actual content of the essential fatty acids in Clinolipid was added to this section.

Clinical Pharmacology

Proposed language deleted to focus primarily on the known metabolism of lipids in humans rather than effects on physiological outcomes.

Nonclinical Toxicology

The principle signs of toxicity identified in the nonclinical review have been noted.

Clinical Studies

Study 1 and 2 as discussed in the Clinical section of this review has been described. Language proposed by the applicant has for the most part been deleted.

Carton and Immediate Container Labels

Recommendations from DMEPA regarding the carton and container labels were sent to the applicant and agreed upon.

12. Recommendations / Risk Benefit Assessment

- **Recommended Regulatory Action**

Approval.

- **Risk Benefit Assessment**

If approved, Clinolipid will be the first intravenous lipid emulsion marketed in the United States for over two decades. Since the approval of Intralipid, other IV lipid emulsions, including Clinolipid (under various foreign brandnames), have become available outside the U.S. The applicant did not submit evidence to this NDA that would suggest Clinolipid has any clinically meaningful advantage over other IV lipid emulsions, including Intralipid or other soy-oil based IV lipid emulsions.

While the review team has little doubt that Clinolipid can be labeled as a source of calories and essential fatty acids in adults, the team did not determine that there is sufficient information to conclude that Clinolipid is safe and effective in children. (b) (4)

[REDACTED] . Uncertainties within the medical and scientific literature on how best to provide essential fatty acids (EFA) and how best to monitor biochemically for EFA deficiency, did not reassure the team that this product could be used safely in pediatric patients. The availability of a soy-oil based IV lipid emulsion in the market, Intralipid, provides reassurance that pediatric patients will still have access to a product in which the concerns over essential fatty acid deficiency do not exist. (b) (4)

[REDACTED] the clinical team was aware of the belief in the medical community that using IV lipid emulsions with lower omega-6 fatty acids could be less pro-inflammatory or less injurious to the liver. Available evidence does not support this assertion. This, in addition to the ongoing shortages in IV lipid emulsion products, raised the serious concern for “off-label” use of Clinolipid in pediatric patients. It was therefore felt to be imperative that postmarket evaluation of Clinolipid in the pediatric population should be performed by the applicant. Such studies, if adequate and well controlled, could serve to support pediatric approval at a later time.

With regard to the phytosterol content of lipid emulsions, considered impurities, the association between phytosterols and liver disease (PNALD) represents a safety concern that requires further evaluation. Based on the information available to date, it appears that Clinolipid, by virtue of being predominantly olive-oil based, has the lowest amount of phytosterols of other soy-based lipid emulsions. This could encourage promotional claims (including parties unassociated with the applicant), although we note that the applicant has not requested such claims in regard to the phytosterol content. Regardless, the role of phytosterols in the development of liver disease or other clinical safety outcomes requires additional evaluation in the post-market setting in patients expected to use this product. At the time of finalization of this review the applicant had agreed to conduct a study to evaluate the role of phytosterols in liver injury.

With regard to the potential for the seal of the bag's administration port to dislodge from the twist off protector assembly and enter the emulsion, there were a number of proposals discussed by the team for dealing with this issue. Ultimately it was felt that incorporating recommendations for avoidance of problematic spike(s) and emphasizing the necessity of in-line filtration into the label, as well as requiring post-market human factors studies, would be sufficient to allow approval.

Clinolipid is a safe product for approval in adults and has the potential to alleviate shortages in the U.S. for IV lipid emulsions. A number of post marketing requirements and commitments have been agreed upon to further characterize the safety of Clinolipid in patient populations anticipated to use the product, including pediatric patients, hospitalized/critical care patients and long-term home care patients.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

A REMS is not recommended for this application.

- **Recommendation for other Postmarketing Requirements and Commitments**

The team's safety concerns, discussed and outlined in this review, were communicated to the applicant prior to approval. Timelines were being negotiated with the applicant at the time of finalization of my review.

Post-Marketing Requirements

- ####-1 Develop and validate an appropriate analytical method for determining the individual component phytosterol content in Clinolipid (lipid injectable emulsion, USP) 20%.
- ####-2 Test the three registration stability batches for the individual component phytosterol content in Clinolipid (lipid injectable emulsion, USP) 20% using the analytical methods developed in PMR ####-1.
- ####-3 Test for the individual component phytosterol content in all batches of Clinolipid (lipid injectable emulsion, USP) 20%, manufactured over a three year period, using the

method developed under PMR #####-1. Based on these test results, establish limits for each of the individual component phytosterols in Clinolipid (lipid injectable emulsion, USP) 20% in the product specification.

- #####-4 Develop and validate an appropriate analytical method for measuring phytosterol levels in plasma.
- #####-5 Conduct a human factors study to assess user comprehension of the label's instructions to use an inline filter with pore size of 1.2 microns during administration of Clinolipid (lipid injectable emulsion, USP) 20% or an admixture containing Clinolipid (lipid injectable emulsion, USP) 20%. In addition, the study should evaluate the ability of the user to appropriately spike the product's administration port. The study should enroll representative user populations, including pharmacists, nurses, and home health care nurses.
- #####-6 Randomized controlled trial to evaluate the risk of developing essential fatty acid deficiency (EFAD) in pediatric patients, including neonates, receiving either Clinolipid (lipid injectable emulsion, USP) 20% or standard of care soybean oil based lipid emulsion. Full essential fatty acid profiles should be evaluated according to standards set by major national reference laboratories. Genetic polymorphisms in the fatty acid desaturase genes (FADS) FADS1 and FADS2 should be determined in at least a subset of patients. The cut-off values for EFAD (e.g., suspected, mild and severe) should be established prior to the study. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR #####-4.
- #####-7 Randomized controlled trial in pediatric patients, including neonates, comparing Clinolipid (lipid injectable emulsion, USP) 20% with a phytosterol-depleted formulation of Clinolipid (lipid injectable emulsion, USP) 20% and another standard-of-care lipid emulsion to evaluate the incidence of liver injury, including either parenteral nutrition-associated liver disease (PNALD) or intestinal failure-associated liver disease (IFALD). This trial should be initiated after the results from PMRs #####-1, #####-2, and #####-6 are available. The phytosterol content of the phytosterol-depleted formulation of Clinolipid (lipid injectable emulsion, USP) 20% should be documented using validated analytical assay methods developed under PMRs #####-1. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR #####-4.

- ####-8 Randomized clinical trial in hospitalized patients receiving either Clinolipid (lipid injectable emulsion, USP) 20% or other standard-of-care IV lipid emulsions to evaluate clinical safety outcomes of sepsis and mortality. In addition, the trial will evaluate the requirement for ventilator support and length of stay in ICU and hospital.
- ####-9 Randomized clinical trial comparing Clinolipid (lipid injectable emulsion, USP) 20% to another standard-of-care IV lipid emulsion, evaluating long-term risk of developing essential fatty acid deficiency (EFAD) and parenteral nutrition associated liver disease (PNALD) in patients receiving chronically-administered total parenteral nutrition (TPN). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR ####-4.

Postmarketing Commitments:

- ####-10 Develop and validate an analytical method for determining cholesterol content in Clinolipid (lipid injectable emulsion, USP) 20%.
- ####-11 Develop and validate an analytical method for determining squalene content in Clinolipid (lipid injectable emulsion, USP) 20%.
- ####-12 Analyze the three registration stability batches for the cholesterol and squalene content, using the analytical methods developed in PMCs ####-10 and ####-11, respectively.
- ####-13 Test all batches of Clinolipid (lipid injectable emulsion, USP) 20% manufactured over a three year period for the cholesterol and squalene content, using analytical methods developed under PMCs #10 and #11, respectively. Based on these test results, establish limits for cholesterol and squalene in the Clinolipid (lipid injectable emulsion, USP) 20% product specification.

• **Recommended Comments to Applicant**

Applicant should be reminded that in their submission dated May 7, 2013, they have committed to file a Prior Approval Supplement to the application to add a comparability protocol for evaluating the effects of changes to the manufacturing process for the Clarity container on extractables from these containers.

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

/s/

ROBERT FIORENTINO
10/03/2013