



NDA 204508

NDA APPROVAL

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) dated and received January 3, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Clinolipid (lipid injectable emulsion, USP), 20%.

We acknowledge receipt of your amendments dated January 24, 2013, February 8, 2013, February 22, 2013, March 15, 2013, March 26, 2013, May 7, 2013, May 15, 2013, May 31, 2013, June 7, 2013, June 25, 2013, August 9, 2013, August 20, 2013, September 12, 2013, September 26, 2013, September 27, 2013, October 1, 2013, October 2, 2013, and October 3, 2013.

This new drug application provides for the use of Clinolipid (lipid injectable emulsion, USP), 20%, in adults for parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

We acknowledge your September 26, 2013, submission containing final printed carton and container labels.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Matthew Brancazio, Pharm.D.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5345
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of liver injury in pediatric patients including neonates, which may be related to the presence of phytosterols, or identify an unexpected serious risk of administration of unfiltered product that contains fragments of the product container.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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

The timetable you submitted on October 2, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/14

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

The timetable you submitted on October 2, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/14

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

The timetable you submitted on October 2, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/16

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

The timetable you submitted on October 2, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/14

- 2085-5 Conduct a human factors study to assess user comprehension of the label's instructions to use an inline filter with pore size of 1.2 microns during administration of Clinolipid (lipid injectable emulsion, USP) 20% or an admixture containing Clinolipid (lipid injectable emulsion, USP) 20%. In addition, the study

should evaluate the ability of the user to appropriately spike the product's administration port. The study should enroll representative user populations, including pharmacists, nurses, and home health care nurses.

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

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

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of essential fatty acid deficiency, or assess a known serious risk of sepsis and mortality with the use of Clinolipid (lipid injectable emulsion, USP) 20%, or identify an unexpected serious risk of liver injury in pediatric patient including neonates, which may be related to the presence of phytosterols.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2085-6 Randomized controlled trial to evaluate the risk of developing essential fatty acid deficiency (EFAD) in pediatric patients, including neonates, receiving either Clinolipid (lipid injectable emulsion, USP) 20% or standard of care soybean oil based lipid emulsion. Full essential fatty acid profiles should be evaluated according to standards set by major national reference laboratories. Genetic polymorphisms in the fatty acid desaturase genes (FADS) FADS1 and FADS2 should be determined in at least a subset of patients. The cut-off values for EFAD (e.g., suspected, mild and severe) should be established prior to the study. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 2085-4.

The timetable you submitted on October 2, 2013, states that you will conduct this trial according to the following schedule:

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

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

USP) 20% should be documented using validated analytical assay methods developed under PMR 2085-1. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 2085-4.

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

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

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

The timetable you submitted on October 2, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/17
Trial Completion: 10/18
Final Report Submission: 04/19

2085-9 Randomized clinical trial comparing Clinolipid (lipid injectable emulsion, USP) 20% to another standard-of-care IV lipid emulsion, evaluating long-term risk of developing essential fatty acid deficiency (EFAD) and parenteral nutrition associated liver disease (PNALD) in patients receiving chronically-administered total parenteral nutrition (TPN). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 2085-4.

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

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

Submit the protocols to your IND 74881 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically

report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2085-10 Develop and validate an analytical method for determining cholesterol content in Clinolipid (lipid injectable emulsion, USP) 20%.

The timetable you submitted on October 2, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/14

2085-11 Develop and validate an analytical method for determining squalene content in Clinolipid (lipid injectable emulsion, USP) 20%.

The timetable you submitted on October 2, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/14

2085-12 Analyze the three registration stability batches for the cholesterol and squalene content, using the analytical methods developed in PMCs 2085-10 and 2085-11, respectively.

The timetable you submitted on October 2, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/14

- 2085-13 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 2085-10 and 2085-11, respectively. Based on these test results, establish limits for cholesterol and squalene in the Clinolipid (lipid injectable emulsion, USP) 20% product specification.

The timetable you submitted on October 2, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/16

Submit chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

ADDITIONAL COMMENTS

We remind you that in your submission dated May 7, 2013, you 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.

If you have any questions, call Matthew Brancazio, Pharm.D., Regulatory Project Manager, at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

Donna Griebel, MD
Director
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s):

Content of Labeling
Carton and Container Labeling

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

/s/

DONNA J GRIEBEL
10/03/2013