NDA 204508/S-022

**SUPPLEMENT APPROVAL**
**POSTMARKETING REQUIREMENT NOT FULFILLED**
**RELEASE FROM POSTMARKETING REQUIREMENT**
**NEW POSTMARKETING REQUIREMENT**

Baxter Healthcare Corporation
Attention: Nicole Rodgers
Senior Manager, Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, IL 60073

Dear Nicole Rodgers:

Please refer to your supplemental new drug application (sNDA) dated June 26, 2023, received June 26, 2023, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Clinolipid (lipid injectable emulsion) for intravenous use.

This Prior Approval sNDA provides for expanding the prescribing information to pediatric patients, including term and preterm neonates, for use as a source of calories and essential fatty acids for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

## APPROVAL & LABELING

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.

## WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## 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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 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 REQUIREMENT NOT FULFILLED

We have received your submission dated June 26, 2023, which contains the final report for the following postmarketing requirement listed in the October 3, 2013, approval letter for this application:

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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.

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

We have reviewed your submission and conclude that the terms of the requirement were not met. This is because the study population did not represent the full range of pediatric age groups, and the duration of treatment was not long enough to include a population at risk for EFAD.

We have determined that the data included in the final report submission does not adequately fulfill the postmarketing requirement. The original milestone due dates were not met, therefore this requirement is considered delayed. This status will be posted on the FDA Postmarketing Requirements and Commitments website.[3]

We remind you that an applicant's failure to comply with the approved timetable, periodic report submissions, and other requirements of section 505(o)(3)(E)(ii) of the FDCA will be considered a violation of that subsection unless the applicant demonstrates good cause for the noncompliance. Under section 505(o)(3)(E)(ii) of the FDCA, FDA will determine what constitutes good cause.

## RELEASE FROM POSTMARKETING REQUIREMENTS

We have received your submission dated June 26, 2023, reporting on the following postmarketing requirement listed in our October 3, 2013, approval letter:

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

[3] http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

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

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

We have reviewed your Annual Report submission dated November 28, 2023, in which you indicate in the Status Report for Postmarket Requirements that for PMR 2085-9, "Baxter requests continued discussion with the Agency to clarify expectations and determine the best way to proceed for establishing milestone dates."

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

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

We have reviewed your submissions and have determined that you are released from the above postmarketing requirements because they are infeasible for the following reasons:

- Regarding PMR 2085-6, the population of study 6344-001, titled *A Randomized, Double-Blind, Controlled, Clinical Trial to Evaluate the Risk of Developing Essential Fatty Acid Deficiency in Pediatric Patients, Including Neonates, Receiving Either Clinolipid (Lipid Injectable Emulsion, USP) 20%*

*or Standard-of-Care Soybean Oil-Based Lipid* did not represent the full range of pediatric age groups, and the duration of treatment was not long enough to include a population at risk for EFAD. Furthermore, we now consider it infeasible to conduct a randomized controlled trial in the treatment population.

- Regarding PMR 2085-9, which was issued with the approval of Clinolipid and required the conduct of a randomized trial to examine the risks of parenteral nutrition-associated liver disease (PNALD) and EFAD in patients receiving chronically administered PN, the study has not been initiated. We now consider it infeasible to conduct a randomized trial in the treatment population.

The above postmarketing requirements will be replaced by the new postmarketing requirement as described below:

**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.

As noted in the October 3, 2013 approval letter, since Clinolipid was approved on October 3, 2013, we determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of the serious risks of EFAD and parenteral nutrition-associated cholestasis (PNAC), the precursor to parenteral nutrition-associated liver disease (PNALD), in pediatric patients of all ages or in adults.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these signals of the serious risks. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4607-1 A single-arm open-label safety trial of Clinolipid to evaluate the risk of developing one or both of the following adverse reactions of essential fatty acid deficiency (EFAD) and parenteral nutrition-associated cholestasis (PNAC) in the following patient populations who are anticipated to need 8 weeks or longer of parenteral nutrition treatment: birth – 2 years, 2 – 11 years, 12 – 17 years, and adults (18 years or older). Plasma fatty acids should be measured using an adequately validated bioanalytical assay method.

The timetable you submitted on March 22, 2024, states that you will conduct this trial according to the following schedule:

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| Draft Protocol Submission | 10/2024 |
| Final Protocol Submission | 04/2025 |
| Trial Completion | 04/2030 |
| Final Report Submission: | 11/2030 |

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 122209 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) 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(a)(1) 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(a)(1) 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.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

*Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]
All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

## PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

## REPORTING REQUIREMENTS

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

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Sydney Rosebraugh, Regulatory Project Manager, at sydney.rosebraugh@fda.hhs.gov or 240-402-2305.

Sincerely,

*{See appended electronic signature page}*

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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JUDITH A RACOOSIN
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