NDA 207648/S-005

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT
RELEASE FROM POSTMARKETING REQUIREMENT

Fresenius Kabi USA, LLC
Attention: Aparna Dagar, PhD, RAC
Senior Director, Regulatory Affairs
Three Corporate Drive
Lake Zurich, IL 60047

Dear Dr. Dagar,

Please refer to your supplemental new drug application (sNDA) dated and received on June 22, 2021, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SMOFlipid (lipid injectable emulsion), 20%.

We acknowledge receipt of your major amendment dated October 21, 2021, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for expanding the indication, dosing, and labeling in pediatric patients of all age groups; postmarketing requirement (PMR) 3002-1, pediatric study, SMOF-018-CP3, entitled, *Prospective, Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare Safety and Efficacy of Smoflipid 20% to Intralipid 20% in Hospitalized Neonates and Infants Requiring 28 Days of Parenteral Nutrition* conducted under Pediatric Research Equity Act (PREA).

APPROVAL & LABELING

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

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

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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).

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated April 30, 2021, containing the final report for the following postmarketing requirement listed in the July 13, 2016, approval letter:

3002-1 A prospective, randomized, controlled, double-blind, parallel-group study to compare the safety and efficacy of SMOFLIPID (lipid injectable emulsion) to standard-of-care soybean oil-based lipid emulsion in hospitalized neonates including low birth weight and very low birth weight neonates. The study must enroll an adequate number of patients who receive parenteral nutrition (PN) for at least 28 days. Continue treatment for all patients who remain on PN for up to 84 days and follow-up 8 days after receiving the last dose of study treatment. The efficacy evaluation should include anthropomorphic measures and the risk of developing essential fatty acid deficiency (EFAD). 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. Secondary endpoints should include incidence of major neonatal morbidities, including BPD (bronchopulmonary dysplasia), ROP (retinopathy of prematurity), IVH (intraventricular hemorrhage), PVL (periventricular leukomalacia), NEC (necrotizing enterocolitis), and late-onset sepsis in premature and low birth weight neonates. The study's safety assessments should include evaluation of the risk of developing parenteral nutritional associated liver

[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.

disease (PNALD) and parenteral nutrition associated cholestasis (PNAC). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 3002-5.

We have reviewed your submission and conclude that the above requirement was fulfilled.

RELEASE FROM POSTMARKETING REQUIREMENT

We have received your submission dated February 5, 2021, containing a request for release of the following PREA postmarketing requirement listed in our July 13, 2016, approval letter:

3002-2 Randomized controlled trial to evaluate the safety and efficacy of SMOFLIPID (lipid injectable emulsion) administered for at least 90 days in pediatric patients, compared to standard of care soybean oil-based lipid emulsion administered for the same duration. Continue treatment for all patients who remain on parenteral nutrition (PN) for up to 1 year. The study should enroll an adequate number of patients 3 month of age and older. The study's efficacy assessments should include anthropomorphic measures and evaluation of the risk of developing essential fatty acid deficiency (EFAD). 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. The study's safety assessments should include evaluation of the risk of developing parenteral nutritional associated liver disease (PNALD) and parenteral nutrition associated cholestasis (PNAC). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 3002-5.

Final Protocol Submission:	5/2017
Study Completion:	11/2020
Final Report Submission:	5/2022

We are also aware that the final protocol for the following FDAAA PMR is due in July 2022.

3002-8 Randomized clinical trial comparing SMOFlipid (lipid injectable emulsion) 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 adult patients receiving chronically administered total parenteral nutrition (TPN). Plasma phytosterol levels

should be assessed in patients using validated analytical assay methods developed under PMR 3002-5.

Final Protocol Submission:	7/2022
Study Completion:	1/2025
Final Report Submission:	1/2026

We anticipate that you will encounter similar problems enrolling this randomized controlled trial (RCT) as you had with the RCT intended to address PREA PMR 3002-2.

We have reviewed your submission and have determined that you are released from the above requirements because they are no longer feasible due to the challenges in enrolling participants and sites.

We remind you that there are postmarketing requirements listed in the July 13, 2016 approval letter that are still open.

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.

Since SMOFlipid was approved on July 13, 2016, we have become aware that there is limited information on the risks of essential fatty acid deficiency (EFAD) and parenteral nutritional-associated cholestasis (PNAC) with long-term use of SMOFlipid (e.g., > 8 weeks). We have also become aware of the presence of an impurity, (b) (4). We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 assess the known serious risks of EFAD and PNAC with longer duration of SMOFlipid treatment, and it will not be sufficient to identify the unexpected serious risk of toxicity that may be associated with exposure to the (b) (4) impurity.

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 the known serious risks of EFAD and PNAC.

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

4240-1 A single-arm open-label safety study of SMOFlipid to evaluate the risk of developing one or both of the following adverse reactions:

- essential fatty acid deficiency (EFAD)
- parenteral nutrition-associated cholestasis (PNAC)

in the following patient populations who are anticipated to need 8 weeks or longer of parenteral nutrition treatment:

- pediatric patients 1 month of age and older; there should be adequate patient representation in each of these age groups: 1 month - 2 years; 2 -11 years; 12-17 years
- adults

The timetable you submitted on March 14, 2022 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2022
Final Protocol Submission:	03/2023
Study Completion:	03/2026
Final Report Submission:	09/2026

You submitted new information about the presence of an impurity, (b) (4) in the drug product. The presence (b) (4) in the drug product was previously unknown. Further, your safety assessment of (b) (4) exposure from SMOFlipid is inadequate, because your (b) (4) toxicity assessment is not justified. Therefore, your safety assessment does not adequately address the potential risk of exposure (b) (4) in SMOFlipid.

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

4240-2 Twenty-eight day intravenous dose-range finding toxicity study of (b) (4) (b) (4) (impurity) in rats to provide a rationale for dose selection and route of administration for the three-month rat toxicity study (PMR 4240-3).

The timetable you submitted on March 14, 2022 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2022
Final Protocol Submission:	10/2022
Study Completion:	02/2023
Final Report Submission:	06/2023

4240-3 Three-month toxicity study of [redacted] (b) (4) (impurity) in rats to support a safety assessment.

The timetable you submitted on March 14, 2022 states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2023
Final Protocol Submission: 10/2023
Study Completion: 02/2024
Final Report Submission: 08/2024

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.[3]

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol(s) to your IND 102137, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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 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.

[3] 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.

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-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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 information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety 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).

REPORTING REQUIREMENTS

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

If you have any questions, call Thao Vu, Sr. Regulatory Project Manager, at (240) 402-2690.

Sincerely,

{See appended electronic signature page}

Joseph G. Toerner, MD, MPH
Director
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

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

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/s/

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