



NDA 207648/Original 1

NDA APPROVAL

Fresenius Kabi USA, LLC
Attention: Lakshmi Rebbapragada
Sr. Regulatory Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Rebbapragada:

Please refer to your New Drug Application (NDA) dated September 25, 2014, received September 26, 2014, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SMOFLIPID (lipid injectable emulsion).

We acknowledge receipt of your major amendment dated June 29, 2015, which extended the goal date by three months.

NDA 207648 provides for the use of SMOFLIPID (lipid injectable emulsion) for the following indications which, for administrative purposes, we have designated as follows:

- NDA 207648/Original 1 - Smoflipid is indicated in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

(b) (4)

The subject of this action letter is NDA 207648/Original 1.

(b) (4)

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 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, text for the 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

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on July 28, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “Final Printed Carton and Container Labels for approved NDA 207648.” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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.

We are deferring submission of your pediatric studies until 2019, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually

according to 21 CFR 314.81 and section 505(a)(3)(C) of the FDCA. These required studies are listed below.

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 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.

The timetable you submitted on July 12, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2015
Study Completion:	10/2018
Final Report Submission:	10/2019

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.

The timetable you submitted on July 12, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2017
Study Completion:	11/2020
Final Report Submission:	11/2021

Submit the protocols to your IND 102137, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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, with the use of SMOFLIPID (lipid injectable emulsion).

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:

3002-3	Test the three registration stability batches for the individual component phytosterol content in SMOFLIPID (lipid injectable emulsion) using the validated analytical methods.
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The timetable you submitted on July 12, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2016

- 3002-4 Test for the individual component phytosterol content in all batches of SMOFLIPID (lipid injectable emulsion) manufactured over a three year period, using the validated analytical method. Based on these test results, establish safety limits for each of the individual component phytosterols in SMOFLIPID (lipid injectable emulsion) product specification.

The timetable you submitted on July 12, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2017

- 3002-5 Develop and validate an appropriate analytical method for measuring phytosterol levels in plasma.

The timetable you submitted on July 12, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2018

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of a serious risk of liver injury including either parenteral nutrition-associated liver disease (PNALD) or intestinal failure-associated liver disease (IFALD) in pediatric and neonatal patients, which may be related to the presence of phytosterols in SMOFLIPID (lipid injectable emulsion). In addition, only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of sepsis and mortality with the use of SMOFLIPID (lipid injectable emulsion). Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of liver injury, parenteral nutrition-associated liver disease (PNALD), and essential fatty acid deficiency (EFAD) with long-term use of SMOFLIPID in adults.

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

- 3002-6 Randomized clinical trial in hospitalized adult patients receiving either SMOFLIPID (lipid injectable emulsion) or other standard-of-care IV lipid emulsions to evaluate clinical safety outcomes of sepsis and mortality. The trial will also evaluate the requirement for ventilator support and length of stay in ICU and hospital.

The timetable you submitted on July 12, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 12/2021
Trial Completion: 12/2024
Final Report Submission: 12/2025

3002-7 Randomized controlled trial in pediatric patients, including neonates, comparing a phytosterol-depleted formulation of SMOFLIPID (lipid injectable emulsion) and another standard-of-care lipid emulsion (100 % soybean oil product) to evaluate the incidence of liver injury, including either parenteral nutrition-associated liver disease (PNALD) or intestinal failure-associated liver disease (IFALD). An adequate number of patients should receive treatment with parenteral nutrition for at least 90 days. This trial should be initiated after the results from PMRs 3002-1, 3002-2, and 3002-3 are available. The phytosterol content of the phytosterol-depleted formulation of SMOFLIPID (lipid injectable emulsion) should be documented using validated analytical assay methods developed under PMR 3002-3. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 3002-5.

The timetable you submitted on July 12, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 07/2022
Trial Completion: 01/2025
Final Report Submission: 01/2026

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.

The timetable you submitted on July 12, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 07/2022
Study Completion: 01/2025
Final Report Submission: 01/2026

Submit the protocol(s) to your IND 102137, with a cross-reference letter to this NDA. Submit 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 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.

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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>.

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).

If you have any questions, call Jacqueline LeeHoffman, Regulatory Project Manager, at (240) 8689.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
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/

JOYCE A KORVICK
07/13/2016