APPLICATION NUMBER:

207648Orig1s000

OTHER REVIEW(S)
MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 20, 2016

TO: File

FROM: Kelly Richards, RN, MSN, Regulatory Health Project Manager

SUBJECT: NDA 207648 Memo of Communication with Fresenius-Kabi

APPLICATION/DRUG: NDA 207648 SMOFlipid

On October 26, 2015, a teleconference was held between the Division of Gastroenterology and Inborn Errors Products (DGIEP) and Fresenius-Kabi (the Sponsor for the application herein referenced).

During this teleconference, the Sponsor was informed that during the review of their submission, it was determined that the fixed-combination rule applied to their application and that they must submit literature on each of the components along with their justification (citing this literature) as to why they believe these components contribute to the safety and efficacy of their product. By virtue of the fact that this product is now relying on literature for approval, the application has now been reclassified from a 505(b)(1) to a 505(b)(2).

The Sponsor agreed to submit the literature as requested and to submit a new FDA Form 356h indicating the application’s new classification as a 505(b)(2).
## RPM FILING REVIEW

( Including Memo of Filing Meeting)
To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

<table>
<thead>
<tr>
<th>Application Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA # 207648</td>
</tr>
<tr>
<td>BLA#</td>
</tr>
</tbody>
</table>

Proprietary Name:  SMOFLipid 20% Lipid Injection Emulsion
Established/Proper Name:  N/A
Dosage Form:  Injection

Strengths:

Applicant:  FRESENIUS KABI USA LLC
Agent for Applicant (if applicable):

Date of Application:  9/25/2014
Date of Receipt:  9/26/2014
Date clock started after UN:

PDUFA Goal Date:  7/26/15
Action Goal Date (if different):  7/24/14
Filing Date:  11/25/14
Date of Filing Meeting:  11/10/2014

Chemical Classification:  (1,2,3 etc.) (original NDAs only)  2
Proposed indication(s)/Proposed change(s):  

Type of Original NDA:
AND (if applicable)

Type of NDA Supplement:

**If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:**
http://inside.fda.gov/CDER/Offices/NewDrugs/ImmediateOffice/UCM07499

Type of BLA

**If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team**

Review Classification:

- Standard
- Priority
- Tropical Disease Priority
- Pediatric Rare Disease Priority
- Review Voucher submitted

Resubmission after withdrawal?  [ ]
Resubmission after refuse to file?  [ ]

Part 3 Combination Product?  [ ]

**If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults**

- Convenience kit/Co-package
- Pre-filled drug delivery device/system (syringe, patch, etc.)
- Pre-filled biologic delivery device/system (syringe, patch, etc.)
- Device coated/imregnated/combined with drug
- Device coated/imregnated/combined with biologic
- Separate products requiring cross-labeling
- Drug/Biologic
- Possible combination based on cross-labeling of separate products

Version: 4/15/2014
Reference ID: 3669187
☐ Other (drug/device/biological product)
☑ Fast Track Designation
☑ Breakthrough Therapy Designation (set the submission property in DARTIS and notify the CDER Breakthrough Therapy Program Manager)
☑ Rolling Review
☑ Orphan Designation
☑ Rx-to-OTC switch, Full
☑ Rx-to-OTC switch, Partial
☑ Direct-to-OTC
☐ PMC response
☐ PRM response:
☐ FDAAA [505(o)]
☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]
☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)
☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Other:

Collaborative Review Division (if OTC product):

List referenced IND Number(s):

<table>
<thead>
<tr>
<th>Goal Dates/Product Names/Classification Properties</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDUFA and Action Goal dates correct in tracking system?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>The priority will update upon 74-day letter and revert to standard.</td>
</tr>
<tr>
<td>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Are the proprietary, established/proper, and applicant names correct in tracking system?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</td>
<td>☒</td>
<td>☐</td>
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</tr>
<tr>
<td>Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://www.fda.gov/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://www.fda.gov/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td>Review priority will update upon entry of 74-day letter to standard.</td>
</tr>
<tr>
<td>If no, ask the document room staff to make the appropriate entries.</td>
<td>☐</td>
<td>☐</td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Application Integrity Policy</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: <a href="http://www.fda.gov/CDER/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/CDER/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If yes, explain in comment column.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If affected by AIP, has OC/OMQ been notified of the submission? If yes, date notified:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>User Fees</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is Form 3397 (User Fee Cover Sheet) included with authorized signature?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>User Fee Status</td>
<td>Payment for this application:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
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<tr>
<td>If a user fee is required and it has not been paid (and it is not exempted or</td>
<td>□ Paid</td>
<td></td>
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</tr>
<tr>
<td>waived), the application is unacceptable for filing following a 5-day grace</td>
<td>□ Exempt (orphan, government)</td>
<td></td>
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</tr>
<tr>
<td>period. Review stops. Send Unacceptable for Filing (UN) letter and contact</td>
<td>□ Waived (e.g., small business, public health)</td>
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<tr>
<td>user fee staff.</td>
<td>□ Not required</td>
<td></td>
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</tr>
<tr>
<td>If the firm is in arrears for other fees (regardless of whether a user fee</td>
<td>□ Not in arrears</td>
<td></td>
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</tr>
<tr>
<td>has been paid for this application), the application is unacceptable for</td>
<td>□ In arrears</td>
<td></td>
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<tr>
<td>filing (5-day grace period does not apply). Review stops. Send UN letter and</td>
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<td>contact the user fee staff.</td>
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</table>

<table>
<thead>
<tr>
<th>505(b)(2) (NDAs/NDA Efficacy Supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application for a duplicate of a listed drug and eligible for approval</td>
<td>□</td>
<td>✗</td>
<td></td>
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<td>section 505(i) as an ANDA?</td>
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<tr>
<td>Is the application for a duplicate of a listed drug whose only difference is</td>
<td>□</td>
<td>✗</td>
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<tr>
<td>that the extent to which the active ingredient(s) is absorbed or otherwise</td>
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<td>made available to the site of action is less than that of the reference listed</td>
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<td>drug (RLD)? [see 21 CFR 314.54(b)(1)].</td>
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<tr>
<td>Is the application for a duplicate of a listed drug whose only difference is</td>
<td>□</td>
<td>✗</td>
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<tr>
<td>that the rate at which the proposed product’s active ingredient(s) is</td>
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<tr>
<td>absorbed or made available to the site of action is unintentionally less than</td>
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<tr>
<td>that of the listed drug [see 21 CFR 314.54(b)(2)]?</td>
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</table>

If you answered yes to any of the above questions, the application may be       |      |     |     |         |
refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review    |      |     |     |         |
staff in the Immediate Office of New Drugs

Is there unexpired exclusivity on any drug product containing the active moiety  | □    | ✗   |     |         |
(e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic  |      |     |     |         |

If yes, please list below:

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Drug Name</th>
<th>Exclusivity Code</th>
<th>Exclusivity Expiration</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

If there is unexpired, 5-year exclusivity remaining on the active moiety for the
proposed drug product, a 505(b)(2) application cannot be submitted until the
period of exclusivity expires (unless the applicant provides paragraph IV patent
certification; then an application can be submitted four years after the date of
approval.) Pediatric exclusivity will extend both of the timeframes in this provision
by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the
approval but not the submission of a 505(b)(2) application.

<table>
<thead>
<tr>
<th>Exclusivity</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does another product (same active moiety) have orphan exclusivity for the same</td>
<td>□</td>
<td>✗</td>
<td></td>
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</tbody>
</table>
indications? Check the Orphan Drug                                                |      |     |     |         |
Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm

<table>
<thead>
<tr>
<th>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</th>
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<tbody>
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</table>

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy

<table>
<thead>
<tr>
<th>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)</th>
</tr>
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<tbody>
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<td>☒</td>
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</table>

If yes, # years requested: 3 years

Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

<table>
<thead>
<tr>
<th>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?</th>
</tr>
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<tbody>
<tr>
<td>☐</td>
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</table>

If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?

If yes, contact the Orange Book Staff (CDER-Orange Book Staff).

<table>
<thead>
<tr>
<th>For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</th>
</tr>
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<tbody>
<tr>
<td>☒</td>
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</table>

If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM

Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

<table>
<thead>
<tr>
<th>Format and Content</th>
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</thead>
<tbody>
<tr>
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</table>

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

Version: 4/15/2014

Reference ID: 3669187
### Overall Format/Content

<table>
<thead>
<tr>
<th>Description</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>If electronic submission, does it follow the eCTD guidance?</td>
<td>☒</td>
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<tr>
<td>If not, explain (e.g., waiver granted).</td>
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<tr>
<td>Index: Does the submission contain an accurate comprehensive index?</td>
<td>☒</td>
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</tr>
<tr>
<td>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</td>
<td>☒</td>
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<tr>
<td>☒ legible</td>
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<tr>
<td>☒ English (or translated into English)</td>
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<tr>
<td>☒ pagination</td>
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<tr>
<td>☒ navigable hyperlinks (electronic submissions only)</td>
<td></td>
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<tr>
<td>If no, explain.</td>
<td></td>
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<tr>
<td>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</td>
<td></td>
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<tr>
<td>If yes, BLA #</td>
<td></td>
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</tbody>
</table>

### Forms and Certifications

*Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

<table>
<thead>
<tr>
<th>Application Form</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</td>
<td>☒</td>
<td></td>
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</tr>
<tr>
<td>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(3)].</td>
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<td></td>
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<tr>
<td>Are all establishments and their registration numbers listed on the form/attached to the form?</td>
<td>☒</td>
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</tbody>
</table>

### Patent Information

*(NDAs/NDA efficacy supplements only)*

<table>
<thead>
<tr>
<th>Description</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</td>
<td></td>
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</table>

### Financial Disclosure

<table>
<thead>
<tr>
<th>Description</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are financial disclosure forms FDA 3454 and/or 3455</td>
<td>☒</td>
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</tbody>
</table>

included with authorized signature per 21 CFR 54.4(a)(1) and (3)?

*Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*

*Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

<table>
<thead>
<tr>
<th>Clinical Trials Database</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is form FDA 3674 included with authorized signature?</td>
<td>☑</td>
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</tr>
<tr>
<td>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</td>
<td></td>
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</tr>
<tr>
<td>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</td>
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</table>

<table>
<thead>
<tr>
<th>Debarment Certification</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a correctly worded Debarment Certification included with authorized signature?</td>
<td>☑</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>Certification is not required for supplements if submitted in the original application; if foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</em></td>
<td></td>
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<tr>
<td><em>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge…”</em></td>
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</table>

<table>
<thead>
<tr>
<th>Field Copy Certification (NDAs/NDA efficacy supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</td>
<td></td>
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<td>☑</td>
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</tr>
<tr>
<td><em>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</em></td>
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<tr>
<td>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</td>
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<table>
<thead>
<tr>
<th>Controlled Substance/Product with Abuse Potential</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
<td></td>
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</tr>
<tr>
<td><em>If yes, date consult sent to the Controlled Substance Staff:</em></td>
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<tr>
<td>For non-NMEs: Date of consult sent to Controlled Substance Staff:</td>
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<td></td>
</tr>
</tbody>
</table>

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Reference ID: 3669187
<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the application trigger PREA?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, notify PeRC RPM (PeRC meeting is required)(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, request in 74-day letter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, request in 74-day letter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BPCA (NDAs/NDA efficacy supplements only):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this submission a complete response to a pediatric Written Request?</td>
<td></td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proprietary Name</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Is a proposed proprietary name submitted?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>REMS</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Is a REMS submitted?</td>
<td></td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, send consult to OSE/DRISK and notify OSE/OSI/DSC/PMSB via the CDER OSI RMP mailbox</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prescription Labeling</strong></td>
<td></td>
<td></td>
<td></td>
<td>Package Insert (PI), Patient Package Insert (PPI), Instructions for Use (IFU), Medication Guide (MedGuide)</td>
</tr>
</tbody>
</table>

\(^2\) [http://inside.fda.gov/9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm](http://inside.fda.gov/9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm)

\(^3\) [http://inside.fda.gov/9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm](http://inside.fda.gov/9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm)
<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carton labels</td>
<td>☑</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Immediate container labels</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Diluent</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Other (specify)</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**Is Electronic Content of Labeling (COL) submitted in SPL format?**

*If no, request applicant to submit SPL before the filing date.*

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**Is the PI submitted in PLR format?**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?**

*If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.*

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**OTC Labeling**

- ☑ Not Applicable

**Check all types of labeling submitted.**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**Is electronic content of labeling (COL) submitted?**

*If no, request in 74-day letter.*

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**Are annotated specifications submitted for all stock keeping units (SKUs)?**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**If no, request in 74-day letter.**

**If representative labeling is submitted, are all represented SKUs defined?**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

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If no, request in 74-day letter.

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Consults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)

If yes, specify consult(s) and date(s) sent:

<table>
<thead>
<tr>
<th>Meeting Minutes/SPAs</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

End-of Phase 2 meeting(s)?
Date(s):

If yes, distribute minutes before filing meeting

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?
Date(s): 4/9/14

If yes, distribute minutes before filing meeting

Any Special Protocol Assessments (SPAs)?
Date(s):

If yes, distribute letter and/or relevant minutes before filing meeting
ATTACHMENT

MEMO OF FILING MEETING

DATE: November 10, 2014

BLA/NDA/Supp #: 207648

PROPRIETARY NAME: SMOFlipid 20% Lipid Injection Emulsion

ESTABLISHED/PROPER NAME: N/A

DOSAGE FORM/STRENGTH: N/A

APPLICANT: FRESENIUS KABI USA LLC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): 

BACKGROUND: SMOFlipid is a mixture of soybean oil \(^{[6][6]}\), Medium Chain Triglycerides \(^{[6][6]}\), olive oil \(^{[6][6]}\) and fish oil \(^{[6][6]}\). This product is approved and in use in Europe and other countries other than the United States.

REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM: Matthew Brancazi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPMS/TL: Wes Ishihara</td>
<td></td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>Ruyi He</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer: Karyn Berry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL: Ruyi He</td>
<td></td>
</tr>
<tr>
<td>Social Scientist Review (for OTC products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OTC Labeling Review (for OTC products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>Clinical Microbiology (for antimicrobial products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td>Department/Function</td>
<td>Reviewer</td>
<td>TL</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>---------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Elizabeth Shang</td>
<td>Sue-Chih Lee</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>Ben Vali</td>
<td>Yeh-Fong Chen</td>
</tr>
<tr>
<td>Nonclinical (Pharmacology/Toxicology)</td>
<td>Emmanuel Akinshola</td>
<td>Sushanta Chakder</td>
</tr>
<tr>
<td>Statistics (carcinogenicity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunogenicity (assay/assay validation) <em>(for BLAs/BLA efficacy supplements)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Quality (CMC)</td>
<td>Tarun Mehta</td>
<td>Marie Kowblansky</td>
</tr>
<tr>
<td>Quality Microbiology <em>(for sterile products)</em></td>
<td>Erika Pfeiler</td>
<td>Marie Kowblansky</td>
</tr>
<tr>
<td>CMC Labeling Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility Review/Inspection</td>
<td>Christina Capacci-Daniel</td>
<td>Mahesh Ramnanadham</td>
</tr>
<tr>
<td>OSE/DMEPA (proprietary name)</td>
<td>Sherly Abraham</td>
<td>Kendra Worthy</td>
</tr>
<tr>
<td>OSE/DRISK (REMS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC/OSI/DSC/PMSB (REMS)</td>
<td>Susan Leienhaut</td>
<td>Susan Thompson</td>
</tr>
</tbody>
</table>
**Bioresearch Monitoring (OSI)**

**Reviewer:**

**TL:**

---

**Controlled Substance Staff (CSS)**

**Reviewer:**

**TL:**

---

**Other reviewers**

PMHS: Peds - Donna Snyder (TL: Hari Sachs) Maternal – Carol Kasten (TL: Alyson Karesh)

OPDP: Meeta Patel

CDRH: Alan Stevens (TL: Keith Marin)

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**Other attendees**

---

**FILING MEETING DISCUSSION:**

**GENERAL**

- 505(b)(2) filing issues:
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
  - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?

  Describe the scientific bridge (e.g., BA/BE studies):

- Per reviewers, are all parts in English or English translation?
  - **If no**, explain:

- Electronic Submission comments
  - **List comments:**

**CLINICAL**

- Comments:

  □ Not Applicable
  □ FILE
  □ REFUSE TO FILE

- Review issues for 74-day letter

---

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| Clinical study site(s) inspections(s) needed? | ☑ YES  
☒ NO |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>If no, explain: TBD</td>
<td></td>
</tr>
</tbody>
</table>
| Advisory Committee Meeting needed?         | ☑ YES  
☒ NO |
| Comments:                                  | Date if known: 
☒ NO  
☒ To be determined |
| If no, for an NME NDA or original BLA, include the reason. For example: | |
| ☐ this drug/biologic is not the first in its class |
| ☐ the clinical study design was acceptable |
| ☐ the application did not raise significant safety or efficacy issues |
| ☐ the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease |
| Abuse Liability/Potential                 | ☑ Not Applicable  
☒ FILE  
☒ REFUSE TO FILE |
| Comments:                                  | ☑ Review issues for 74-day letter |
| If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? | ☑ Not Applicable  
☒ YES  
☒ NO |
| Comments:                                  |                  |
| CLINICAL MICROBIOLOGY                     | ☑ Not Applicable  
☒ FILE  
☒ REFUSE TO FILE |
| Comments:                                  | ☑ Review issues for 74-day letter |
| CLINICAL PHARMACOLOGY                     | ☑ Not Applicable  
☒ FILE  
☒ REFUSE TO FILE |
| Comments:                                  | ☑ Review issues for 74-day letter |
| Clinical pharmacology study site(s) inspections(s) needed? | ☑ YES  
☒ NO |
| BIOSTATISTICS                              | ☑ Not Applicable  
☒ FILE |

Reference ID: 3669187
| Comments: | REFUSE TO FILE □ | Review issues for 74-day letter □ |
| NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) | Not Applicable □ | FILE □ | REFUSE TO FILE □ |
| Comments: | Review issues for 74-day letter □ |
| IMMUNOGENICITY (BLAs/BLA efficacy supplements only) | Not Applicable □ | FILE □ | REFUSE TO FILE □ |
| Comments: | Review issues for 74-day letter □ |
| PRODUCT QUALITY (CMC) | Not Applicable □ | FILE □ | REFUSE TO FILE □ |
| Comments: | Review issues for 74-day letter □ |
| **Environmental Assessment** | | | |
| • Categorical exclusion for environmental assessment (EA) requested? |
|   If no, was a complete EA submitted? |
|   If EA submitted, consulted to EA officer (OPS)? |
| Comments: | YES □ | NO □ |
| **Quality Microbiology (for sterile products)** | Not Applicable □ | YES □ | NO □ |
| • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) |
| Comments: Information requests in 74-day letter |

Reference ID: 3669187
<table>
<thead>
<tr>
<th>Table: Facility Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Establishment(s) ready for inspection?</td>
</tr>
<tr>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>√ YES</td>
</tr>
<tr>
<td>□ NO</td>
</tr>
<tr>
<td>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</td>
</tr>
<tr>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>√ YES</td>
</tr>
<tr>
<td>□ NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table: Facility/Microbiology Review (BLAs only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments:</td>
</tr>
<tr>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>√ FILE</td>
</tr>
<tr>
<td>□ REFUSE TO FILE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table: CMC Labeling Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments:</td>
</tr>
<tr>
<td>□ Review issues for 74-day letter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table: APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</td>
</tr>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>□ No</td>
</tr>
<tr>
<td>• If so, were the late submission components all submitted within 30 days?</td>
</tr>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>□ No</td>
</tr>
<tr>
<td>• What late submission components, if any, arrived after 30 days?</td>
</tr>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>□ No</td>
</tr>
<tr>
<td>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</td>
</tr>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>□ No</td>
</tr>
</tbody>
</table>
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?  
  ✔️ YES  
  ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?  
  ☐ YES  
  ☒ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Joyce Korvick, M.D., M.P.H.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be suitable for filing.

Review Issues:

☐ No review issues have been identified for the 74-day letter.

☐ Review issues have been identified for the 74-day letter. List (optional):

Review Classification:

☒ Standard Review

☐ Priority Review

ACTIONS ITEMS

☒ Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).

☐ If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

☐ If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

☐ BLA/BLA supplements: If filed, send 60-day filing letter

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<table>
<thead>
<tr>
<th>If priority review:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</td>
</tr>
<tr>
<td>• notify OMPQ (so facility inspections can be scheduled earlier)</td>
</tr>
<tr>
<td>Send review issues/no review issues by day 74</td>
</tr>
<tr>
<td>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</td>
</tr>
<tr>
<td>Update the PDUFA V DARRTS page (for NME NDAs in the Program)</td>
</tr>
<tr>
<td>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">These sheets may be found in the CST eRoom at: [http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</a></td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW B BRANCAZIO
12/08/2014

Reference ID: 3669187
Division of Pediatric and Maternal Health Review

Date: September 23, 2015  Consult Received: October 8, 2014

From: Carol H. Kasten, MD, Medical Officer
Division of Pediatric and Maternal Health,
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Acting Team Leader
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Acting Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Gastroenterology and Inborn Errors Products

Drug: Smoflipid 20% (lipid injectable emulsion) for intravenous use
(NDA 207-648, IND 102-137)

Proposed Indication: (b)(4)

Subject: Labeling Review

Sponsor: Fresenius Kabi USA, LLC

Consult Request: “Please participate in the review of the submitted material including studies and labeling.”

Materials Reviewed:
- Smoflipid NDA application documents
- May 6, 2014 PMHS Maternal Health Team review of Kabiven/Perikabiven,
  Carrie Ceresa, PharmD, primary author, DARRTS Reference ID 3501609.
INTRODUCTION
This NDA was submitted by Fresenius Kabi USA, LLC as a new molecular entity (NME). Smoflipid has been marketed for adult patients in the European Union (EU) since 2004. The Division of Gastroenterology and Inborn Errors Products (DGIEP) met with the applicant on July 1, 2008, to discuss their plans for this NME. There were several additional meetings with Fresenius Kabi leading up to the submission of this NDA in September 25, 2014. On October 8, 2014, DGIEP consulted the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH) to review and provide labeling recommendations for the Pregnancy (subsection 8.1) and Lactation (subsection 8.2) for Smoflipid.

BACKGROUND
Lipid Infusions
A lipid infusion drug product is used in conjunction with amino acids, electrolytes, trace elements and dextrose infusions to provide total parenteral nutrition (TPN). Lipid infusions are intended to provide calories and should constitute no more than 60% of a patient’s total caloric intake. Current dietary guidelines from the United States Department of Agriculture (USDA) recommend that fats should comprise between 20 and 35% of an adult’s daily caloric intake. Lipid infusions are also intended as a source of essential fatty acids when a patient is deficient.

Intralipid 20%, Nutrilipid 10% or 20%, Clinolipid 20% and Kabiven all have soybean oil as their primary source of fatty acids. Given the similarity between Smoflipid 20% and Intralipid 20%, some details on use of Intralipid 20% will be discussed in this review for background purposes only.

Smoflipid is a 20% lipid drug product composed of lipids from soybean oil (6%), medium chain triglycerides (6%), olive oil (5%), and fish oil (3%). Smoflipid was submitted as a combination drug and device product. The device is a single chamber

<table>
<thead>
<tr>
<th>FDA-Approved lipid Infusions</th>
<th>NDA</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Intralipid 20%</td>
<td>NDA 18-449</td>
<td>January, 1981</td>
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<tr>
<td>Nutrilipid 10% &amp; 20%</td>
<td>NDA 019-531</td>
<td>May, 1993</td>
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<td>Clinolipid 20%</td>
<td>NDA 204-508</td>
<td>October, 2013</td>
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<tr>
<td>Kabiven¹</td>
<td>NDA 200-656</td>
<td>August, 2014</td>
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</tbody>
</table>

³ See Clinical Pharmacology online.
⁴ Kabiven is a drug – device combination product which has Intralipid as its lipid source as well as amino acids, trace elements and dextrose for complete nutrition.
flexible plastic IV bag which has been approved for use with other lipid infusion products.

Nutritional Requirements during Pregnancy
Guidelines from the Institute of Medicine recommend an optimal amount of weight to be gained during pregnancy based on the woman’s pre-pregnancy body-mass index with adjustments for multifetal gestations. A woman whose BMI is in the normal range (18.5 – 24.9 kg/m²) should gain between 25 and 35 pounds during pregnancy. As noted above, fatty acids are an integral part of the caloric intake of adults and are required during pregnancy for normal fetal and placental growth. Development of the fetal central nervous system requires variety of essential fatty acids including docosahexanoic acid and arachidonic acid. The placenta also has a high lipid requirement much of which is used for phospholipids to produce the placental structure.

Practice Guidelines for Parenteral Nutrition
Few pregnant women will require use of TPN with a lipid infusion such as Smoflipid; however, the American College of Obstetrics and Gynecology (ACOG) supports use of TPN when both anti-emetic medications and enteral feedings via naso-gastric tube have failed to maintain the pregnant woman’s weight in patients with hyperemesis gravidarum.

Nausea and Vomiting in Pregnancy
In early pregnancy, approximately half of all pregnant women have nausea and vomiting. For a third of these pregnant women, their nausea and vomiting becomes clinically significant. Rarely, as in the case of hyperemesis gravidarum (HG), some pregnant women’s symptoms are so severe as to cause dehydration, ketonuria, hypokalemia and weight loss of 5% or more of the woman’s presymptomatic weight. The causes of nausea and vomiting in pregnancy are not known although there are several theories. Changes in a pregnant woman’s symptom severity have been associated with the rise and fall of her human chorionic gonadotropin levels. It has also been suggested that vitamin B deficiency may play a role in inducing nausea and vomiting as vitamin B containing medications reduce its severity. Lastly, there are a few reports

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5 Institute of Medicine; DRI Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC, The National Academies Press, 2011
8 See Brenna et al.
9 See Brenna et al.
12 See Niebyl.
13 See Niebyl.
14 See ACOG Practice Bulletin.
15 See Niebyl.
which have associated HG with elevated levels of fetal DNA in the maternal blood suggesting damage to the feto-maternal barrier.\textsuperscript{16,17}

A meta-analysis of studies, examining the impact of HG on birth outcomes by Veenendaal, \textit{et al.}, found that women with HG were more likely to deliver a low birth weight (LBW)\textsuperscript{18} baby (OR 1.42; 95% CI 1.21 – 1.58). Infants of mothers with HG are also slightly more likely to be small for gestational age (SGA)\textsuperscript{19} (OR 1.28; 95% CI 1.02 – 1.60) as well as premature\textsuperscript{20} (OR 1.32; CI 1.04-1.68).\textsuperscript{21} An analysis from the Norwegian Mother and Child Birth Cohort Study evaluated 814 HG pregnancies of the almost 72,000 pregnancies born between 1998 and 2008.\textsuperscript{22} Unlike the meta-analysis of Veenendaal, \textit{et al.}, no association was found between HG pregnancies and the possible outcomes of LBW, SGA or premature birth. Limitations of both these publications are neither reported whether TPN was used to treat pregnant women with HG. Nor did either publication compare the pregnancy outcomes of HG women treated with TPN to HG women not treated with TPN.

\textit{Reviewer comments:}
\textit{The publications above were not intended to evaluate the safety or efficacy of TPN in the treatment of HG. Rather, the articles examined the consequences of the disease itself irrespective of interventions. HG is a rare clinical event which must be evaluated and treated based on the individual woman’s clinical findings. For some pregnant patients treatment with TPN may be required for the health of the mother and her fetus.}

\textbf{REVIEW}

\textbf{Pregnancy and Lactation Databases Review}

To provide information on possible risks posed by use of these lipid infusions during pregnancy or lactation the toxicology databases Reprotox,\textsuperscript{23} TERIS,\textsuperscript{24} Shepard’s,\textsuperscript{25} and

\textsuperscript{16} Sekizawa A, Sugito Y \textit{et al.}, Cell-free Fetal DNA Is Increased in Plasma of Women with Hyperemesis Gravidarum; Clin Chem. 2001; 47:2164-2165.


\textsuperscript{18} Low birth weight is defined as a birthweight less than 2.5 kg.

\textsuperscript{19} Small for gestational age is defined as a birthweight less than the 10\%ile for gestational age.

\textsuperscript{20} Premature birth is defined as a birth at less than 37 weeks gestation.


\textsuperscript{23} Reprotox® Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed June 4, 2015.

\textsuperscript{24} TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. [http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidenceexpert/ND_PR/evidenceexpert/CS/](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidenceexpert/ND_PR/evidenceexpert/CS/). Accessed 3/21/2014

\textsuperscript{25} © 2014 Shepard's: A Catalog of Teratogenic Agents: An updated, automated version of Shepard's Catalog of Teratogenic Agents is distributed with TERIS. It’s a comprehensive compilation of animal and human research on the teratogenicity of chemical and environmental agents. The Catalog contains
LACTMED®, were searched and no reviews were found on Smoflipid or Intralipid 20%.

**Treatment with Total Peripheral Nutrition during Pregnancy**

There are a few reports of pregnant women treated with TPN for HG, pre-existing disease or new onset disorders. One publication in particular is a retrospective study of 26 pregnant women treated with TPN at Thomas Jefferson University Hospital between 1990-1997. Note that the TPN products were not identified. Women in the study suffered from HG (n=16), cholecystitis/pancreatitis (n=3), small bowel obstruction (n=2), intracranial bleed (n=2), ulcerative colitis (n=1) and other disorders (n=2). The mean gestational age at initiation of TPN was 16.2 weeks and mean duration of TPN administration was 31 days. Five pregnancies were terminated prior to fetal viability. There were 9 premature deliveries, two of which were idiopathic. The remaining premature deliveries were associated with multiple gestations, cholecystitis, preeclampsia, premature rupture of membranes or a history of recurrent premature delivery. One infant was born SGA and another was macrosomic. The study’s primary finding was that centrally inserted catheters had a high rate of complications relative to peripherally inserted central catheters (50% vs. 9%). The authors concluded that pregnant women requiring treatment with TPN can have successful birth outcomes and peripherally inserted central catheters appear to have fewer complications than those centrally inserted.

**DISCUSSION**

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are

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26 LACTMED® The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 990; Last Revision Date: 20130907


30 See Russo-Stieglitz et al.

31 See Russo-Stieglitz et al.

32 Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).
subject to the 2006 Physicians Labeling Rule\textsuperscript{33} format to include information about the risks and benefits of using these products during pregnancy and lactation.

Pregnancy Labeling
No animal reproduction or lactation studies with Smoflipid were submitted by the applicant and no reviews of Smoflipid or Intralipid 20\% use in pregnancy are available to consider in the toxicology databases. One small retrospective study does suggest that use of TPN with a lipid infusion, when a pregnant woman cannot maintain her weight, can have beneficial effects.\textsuperscript{34} As noted above, ACOG practice guidelines support the use of TPN which includes use of lipid infusions for treatment of a pregnant woman when both anti-emetic medications and enteral feedings via naso-gastric tube have failed to maintain the pregnant woman’s weight.\textsuperscript{35} DPMH recommends labeling language for 8.1 which conveys the paucity of clinical trial data on the benefit–risk of TPN administration during pregnancy; however, the labeling should also include a Clinical Considerations section that describes the use of TPN with a lipid infusion in instances where pregnant women are unable to consume adequate nutrients to maintain their weight.

Lactation Labeling
There are no data on the safe use of TPN during lactation nor are there reports of serious adverse events. Therefore, the benefits of breastfeeding should be considered in a lactating woman receiving TPN. DPMH recommends labeling language which conveys to healthcare providers the need for a benefit/risk assessment of Smoflipid use during lactation.

DPMH attended meetings with DGIEP from November 2014 through August 2015. DPMH presented its labeling recommendations at the June 9, 2015 meeting with the DGIEP.

CONCLUSIONS
\begin{itemize}
  \item There are no data on Smoflipid use during pregnancy or lactation to inform a benefit/risk assessment.
  \item Limited clinical data on use of other lipid infusions and practice guidelines from ACOG support use of TPN with a lipid infusion in the rare instances where a pregnant woman is unable to consume sufficient nutrients to maintain her weight.
  \item There are no data on the use of TPN and lipid infusions during breastfeeding. However, there are no serious adverse events in adult patients identified that would warrant limitation of breastfeeding.
\end{itemize}

\textsuperscript{33} Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

\textsuperscript{34} See Russo-Steiglitz, et al.

RECOMMENDATIONS
The following are the DPMH Maternal Health Team recommendations for the proposed labeling for Smoflipid. Language was provided in the following sections of the Smoflipid labeling:

SMOFLIPID (lipid injectable emulsion) 20%, for intravenous use

Full Prescribing Information: Contents*
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data Animal reproduction studies have not been conducted with SMOFLIPID. It is not known whether SMOFLIPID can cause fetal harm when administered to a pregnant woman. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Severe malnutrition in a pregnant woman is associated with preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality. Parenteral nutrition should be considered if the pregnant woman’s nutritional requirements cannot be fulfilled by oral or enteral intake.

8.2 Lactation
Risk summary
No data are available regarding the presence of SMOFLIPID in human milk, the effects on the breast fed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SMOFLIPID and any potential adverse effects on the breastfed infant from SMOFLIPID or from the underlying maternal condition.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL H KASTEN
09/23/2015

TAMARA N JOHNSON
09/23/2015

LYNNE P YAO
09/23/2015
Memorandum

Date: June 29, 2015

To: Matthew Brancazio, Pharm.D., MBA, Regulatory Health Project Manager Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Pharm.D., RAC, Team Leader, Office of Prescription Drug Promotion (OPDP)

Subject: NDA 207648 – SMOFLIPID (lipid injectable emulsion), for intravenous use

Reference is made to DGIEP’s consult request dated October 7, 2014, requesting review of the proposed Package Insert (PI), Patient Package Insert (PPI), and Carton/Container Labeling for SMOFLIPID (lipid injectable emulsion), for intravenous use (Smoflipid).

OPDP has reviewed the proposed PI entitled, “Smoflipid.draftPI.word.clean from sponsor.1.15.15” that was sent via email from DGIEP to OPDP on June 16, 2015. OPDP’s comments on the proposed PI are provided directly below.

We note that a PPI is no longer being developed for this product, and therefore we have not reviewed this document.

OPDP has also reviewed the following proposed carton/container labels submitted by the sponsor on March 19, 2015 (attached below) and available in the EDR, sequence 0010:

- Fk-draft-100ml-container.pdf
- Fk-draft-250ml-container.pdf
- Fk-draft-500ml-container.pdf

We note that the three proposed container labels are very similar, and would defer to DMEPA regarding the adequacy of these labels to appropriately distinguish between the three container sizes (i.e., 100ml, 250ml, and 500ml).

Thank you for your consult. If you have any questions please contact Kathleen Klemm at Kathleen.klemm@fda.hhs.gov or 301-796-3946.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHLEEN KLEMM
06/29/2015
CLINICAL INSPECTION SUMMARY

DATE: June 11, 2014

TO: Matthew Brancazio, Regulatory Project Manager  
Karyn Berry, M.D., Medical Officer  
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.  
Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207648

APPLICANT: Fresenius Kabi USA, LLC

DRUG: Smoflipid 20%

NME: No

THERAPEUTIC CLASSIFICATION: Standard
CONSULTATION REQUEST DATE: January 23, 2015
INSPECTION SUMMARY GOAL DATE: June 21, 2015
DIVISION ACTION GOAL DATE: July 24, 2015
PDUFA DATE: July 26, 2015

I. BACKGROUND:

Fresenius Kabi USA, LLC submitted this NDA for the indication...

Lipid emulsions are a necessary component of PN, and have two main functions: a supply of energy, and a supply of essential fatty acids.

According to the applicant, SMOF (soybean oil, medium chain triglycerides [MCT], olive oil and fish oil) 20% is a lipid emulsion for intravenous injection. The clinical trials submitted in this application had been conducted between September 1997 and February 2006. The product was approved by Sweden as the EU Reference Member State (RMS) in 2004, followed by a Mutual Recognition Procedure (MRP) in Europe. Approval for use in pediatric patients was obtained in Europe in September 2009. None of the studies were conducted under a U.S. IND.

The review division requested inspection of the clinical trials below that were submitted in support of the indication. All the trials except Protocol 03-SMOF-005 and Protocol FE-SM-03-DE were single site trials. Both Dr. Devleger’s site for Protocol 03-SMOF-005 and Dr. Grimm’s site for FE-SM-03-DE were chosen on the basis of high enrollment.

1. Protocol 03-SMOF-005 entitled “A randomized, double-blind study evaluating the safety, tolerability and efficacy of SMOFlipid 20% compared to Intralipid 20% in premature infants” was conducted from May 2004 to February 2006.

2. Protocol 00-SMOF-004 entitled “A randomized, double-blind study evaluating the safety, tolerability and efficacy of SMOF 20% compared to Intralipid 20% in premature infants” was conducted from April 2004 to February 2006.

3. Protocol 00-SMOF-002 entitled “A randomized, double-blind study of safety and efficacy of SMOF 20% vs Intralipid 20% in infants and children requiring long-term parenteral nutrition.” was conducted from May 2003 to March 2005.


II. RESULTS (by Site):

<table>
<thead>
<tr>
<th>Type of Inspected Entity, Name, and Address</th>
<th>Protocol #/ Site #/ # of Subjects/Dates of Study Conduct</th>
<th>Inspection Date</th>
<th>Classification*</th>
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<tbody>
<tr>
<td>CI: Prof. Dr. Hugo Devlieger</td>
<td>03-SMOF-005/ Site 2/ 53 subjects/ May 2004 to February 2006</td>
<td>April 27 to 30 and May 5 to 8, 2015</td>
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<td>Universitaire Ziekenhuizen Leuven</td>
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<td>Dept. of Neonatology</td>
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<td>Herestraat 49, B-3000 Leuven, Belgium</td>
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<td>CI: Dr. Erika Tomsits</td>
<td>00-SMOF-004/ Single site/ 60 subjects/ April 2004 to February 2006</td>
<td>May 11 to 14, 2015</td>
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<td>Semmelweis University Second Department of Paediatrics</td>
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<td>Tûzoltó U. 7-9, H-1094 Budapest, Hungary</td>
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<td>CI : Prof. Olivier Goulet</td>
<td>00-SMOF-002/ Single site/ 28 subjects/ May 2003 to March 2005</td>
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<td>University of Paris</td>
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<td>149 Rue de Sèvres, 75743 Paris Cedex 5, France</td>
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<td>Clinic for General and Thoracic Surgery of the Center for Surgery</td>
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<td>Justus-Liebig University</td>
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<td>Rudolph-Buchheim-Str. 7 D-35385 Giessen, Germany</td>
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<td>Head, Clinical Nutrition University Hospital</td>
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<tr>
<td>Rue Micheli-du-Crest 24, CH-121 1 Geneva, Switzerland</td>
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Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.
1. Prof. Dr. Hugo Devlieger
Universitaire Ziekenhuizen Leuven, Dept. of Neonatology
Leuven, Belgium

Note: Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

a. **What was inspected:** This is one of two enrolling sites, for Protocol 03-SMOF-005. There were 54 subjects screened at the site, and 53 subjects were enrolled. The records for all 53 subjects were reviewed. A total of 45 subjects completed the study. The inspection included review of informed consent documents (ICDs), Ethics Committee correspondence and approvals, source documents including hospital records, sponsor correspondence, and adverse event reports.

b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. Data for height, weight, adverse events, protocol deviations, and other listings could be verified. Discontinuations were accurately categorized in the line listings and included deaths, withdrawal of consent, and increased enteral feedings.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Dr. Erika Tomsits
Semmelweis University, Second Department of Pediatrics, Budapest, Hungary

Note: Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

a. **What was inspected:** This is the single enrolling site for Protocol 00-SMOF-004. A total of 60 subjects were screened and enrolled at the site, and a total of 51 subjects completed the study. Records for 24 subjects were reviewed. The inspection included review of informed consent documents (ICDs), Ethics Committee correspondence and approvals, source documents including hospital records, sponsor correspondence, case report forms (CRFs), and adverse event reports.

b. **General observations/commentary:** This study was conducted from April 2004 to February 2006. There was no underreporting of adverse events and the primary efficacy data were verifiable. Although no violations were cited and a Form FDA 483 was not issued, the FDA field investigators noted the following
in an e-mail communication:

1. One medical file was missing, that of Subject 202 who had been randomized to the SMOF lipid group. This subject completed the study and had an AE of fever on Day 7. A violation was noted in the line listings that the subject had been allocated to an incorrect stratum.

**Reviewer note:** Concerning the protocol deviation for Subject 202: Based on weight, the subject was supposed to be allocated to Strata 3 instead of Strata 2, but the subject was allocated to treatment for Strata 2 (lower dose), so a deviation was reported by the site. Dr. Tomsits stated that she decided to put the subject in the lower dose group (Strata 2) because the baby weight was borderline and she felt that it was safer for the baby to receive the lower dose.

2. The site did not keep detailed records related to study drug accountability. The only evidence showing that the infusion pertaining to the study drug was completed is that Dr. Tomsits wrote in the patient’s medical file “SMOF” to refer to the study drug, regardless of the treatment assigned to the subject (SMOF 20% vs Intralipid).

**Reviewer note:** Section 7.5 of the protocol stated: “The use of the investigational and reference medication must be documented per subject in the CRF and on the drug accountability lists.” However, there was no place in the CRF to provide this documentation. There was no drug accountability log available for review at this site. Dr. Tomsits stated that the study drug was received and returned by the pharmacy. During the inspection, the CI could not recall if the pharmacy kept copies of drug accountability records.

3. Some discrepancies between the data listing and the source documents were noted and include:
   a. Subject No. 310 (randomized to SMOF): Discrepancy –Laboratory Efficacy Pre-Study Period (Day 0).
      i. Data listing for RBC fatty acid pattern (n6 fatty acids), specifically, Oleic acid C18:1 n9 reads 30.50. The source document reads 307.50.
      ii. Data listing for RBC fatty acid pattern (n3 fatty acids), specifically, Docosahexaenoic acid C22:6 n3 reads 130.10. The source document reads 130.12.
   b. Subject 209 (randomized to SMOF): Discrepancy in body weight day 4:
      i. Data listing reads 1716. Source documents read 1710.
   c. **Assessment of data integrity:** This study was conducted ten years ago and was not conducted under IND. Issues noted above were considered not to have impact on overall data reliability. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.
3. Prof. Olivier Goulet  
Hôpital Necker-Enfants Malade, University of Paris, Paris, France

a. What was inspected: This was the single site for Protocol 00-SMOF-002. The study was conducted from May 2003 to March 2005. A total of 28 subjects were screened, enrolled, and completed the study. Source documents for all subjects were available for review.

b. General Observations/Commentary: The records were well organized and legible. All records were available for review upon request. The primary efficacy data were able to be verified. The study was well monitored and no information/records were missing. All protocol deviations and adverse events were reported in the line listings submitted by the sponsor to the NDA.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

4. Prof Helmut Grimm  
Clinic for General and Thoracic Surgery of the Center for Surgery  
Justus-Liebig University, D-35385 Giessen, Germany

Note: Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

a. What was inspected: The study was conducted from September 1997 to July 1998. At this site, for Protocol FE-SM-03-DE, 48 subjects were screened and 46 subjects enrolled into the study. A total of 35 subjects completed the study. A total of 28 subject records were reviewed. Source documents including hospital charts and informed consent documents were reviewed. None of the pages of the CRFs that were completed by the site were available at the site. The sponsor brought certified copies of the original CRFs to the site during the inspection.

b. General Observations/Commentary: Eleven of 48 medical files were missing. These included the following six subjects randomized to SMOF: 9067, 9115, 9186, 9190, 9260, and 9283; three subjects randomized to Lipovenos: 9069, 9228, and 9233; and both of the screen failures: 9068 and 9229. When questioned about the loss of the records, Dr. Grimm explained that the files were stored at the hospital when he worked there. After he left this location about 13 years ago to work at another hospital, the University Hospital of Giessen underwent a merger with another hospital in 2005. When the merger
occurred, the medical records were sent to an outside storage location. Dr. Grimm believes that the missing files were either misplaced or not kept by the hospital after the hospital merge took place. He also stated that under German law all records should be kept for 10 years and that this was beyond the limit.

**Reviewer note:** The missing records appear to have been lost due to the age of the study. There is no pattern in which records were missing to indicate suspicion of fraud.

There was no evidence of underreporting of adverse events. The laboratory results available at the site were obtained at a local laboratory and were consistent with the laboratory results in the CRFs. However, the laboratory results in the source documents and CRFs did not match the data listings because the values in the data sets submitted to FDA were obtained at a central laboratory and were not sent to the clinical sites.

**Reviewer note:** The absence of source data for an endpoint that is determined centrally is a common occurrence, so inability to verify source data does not indicate that the data are unreliable.

The site had certified copies of the CRF on which labels of the study drug administered to the subject were affixed. The medical files (source documents) showed that the infusions pertaining to the study drug were performed. Dr. Grimm stated that the nurses wrote in the patient’s medical file when the infusions were done and that sometimes the nurses wrote “Dr. Grimm Study” in the patient medical record to refer to the study drug, regardless of the treatment assigned to the subject (SMOF 20% vs Intralipid).

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

5. Dr. Claude Pichard  
   Head, Clinical Nutrition, University Hospital  
   Geneva, Switzerland

**Note:** Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

a. **What was inspected:** This was the single enrolling site for Protocol FE-SM-04-CH. The study was conducted from January 1998 to August 1998. A total of 32 subjects were screened at the site and 32 subjects were enrolled and received study medication. Twenty subjects completed the study. All 32 subjects’ enrolled had informed consent documents available for review. A total of 27 subjects had all source documentation available for review, including primary and secondary endpoint data. Two subjects had some source data, but source data were missing for laboratory values for primary endpoint triglyceride values. Three subjects did not have any source documentation available for
review. Case report forms for all subjects were available for review. 

**Reviewer note:** Professor Pichard stated that per Swiss law they were not required to maintain records for this long, as the study was conducted in 1998. According to Dr. Pichard, Swiss law requires that the records be maintained for 15 years. They found what records they could. It was not known at the time the study was conducted, that the data would be submitted by the sponsor in the future; therefore, not all records were archived.

b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. Data listings could be verified for the existing source records for the 27 subjects. The source documentation that was available was well organized and in good condition. Swiss law requires that records be maintained for 15 years after the completion of the study and this had passed in 2013, so an FDA 483 was not issued for missing records.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical investigator sites were inspected for this application. All reviews except Dr. Goulet are preliminary and based on e-mail communications. All of the inspections have a preliminary classification of NAI. Dr. Devlieger and Goulet had no issues noted on inspection. For the other investigators, there were issues with missing records and lack of adequate drug accountability. At Dr. Grimm’s site, of the 46 subjects enrolled, records were present 37 subjects. At Dr. Pichard’s site, records were present for 27 of the 32 subjects enrolled. At Dr. Tomsits’ site there was 1 record missing of the 60 subjects enrolled. The occurrences of missing records are consistent with the age of the trials. There did not appear to be any systematic violations or evidence of fraud or any activities that would endanger subject safety. In discussions with FDA field investigators, they were reluctant to issue Forms FDA 483 for the issues noted above due to the age of the studies and the fact that these studies were not conducted under a US IND.

The studies appear to have been conducted adequately, and the data generated by the study appear acceptable in support of the respective indication.
Clinical Inspection Summary

Product: Smoflipid 20%
Sponsor: Fresenius Kabi USA, LLC

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Medical Reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Reference ID: 3778735
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN LEIBENHAUT
06/12/2015

SUSAN D THOMPSON
06/15/2015

KASSA AYALEW
06/15/2015
CONSULT REVIEW

Date: February 18, 2015

From: William M. Burdick, Biomedical Engineer/Physicist
CDRH/ODE/DAGID, General Hospital Device Branch

To: Matthew Brancazio, Sr. Program Management
CDER/OND/ODEIII/DGIEP

Through: Alan Stevens, Combination Products Liaison
CDRH/ODE/DAGRID, General Hospital Device Branch

Through: Richard Chapman, Branch Chief
CDRH/ODE/DAGRID, General Hospital Device Branch

Subject: ICC1400638: NDA207648-SMOFlipid administered via (b)(4) bag: Assessment of Response to 12-15-14 Engineering Review Deficiencies regarding (b)(4) Bag

NOTE: The following issues were not addressed in this review:

- Sterilization
- Biocompatibility
- Material composition
- Drug stability
- Leachables and extractables

There are many more scientists in CDER with the expertise to appropriately address these issues than are employed in CDRH; therefore, CDRH defers to CDER regarding the review of such issues.

PREVIOUS ENGINEERING REVIEW

The NDA did not address any engineering-related issues concerning the container-closure system, the (b)(4) bag. Therefore, my review contained just the following request for additional information:

Please clearly cite the container closure device/system for your drug product and include pictures, engineering drawings/schematics, etc. In your submission you cited both three chamber and one chamber (b)(4) reservoir/IV bags as your container closure device.

In addition, please provide all processing and bench testing to which your final finished device was subjected including all strength of material testing. The description of the strength and material testing should include the test name, test pre-conditions and actual test conditions, the test protocol, the names of all apparatus employed in the testing along with last dates of calibration, past/fail criteria, and test results. You may substitute specifications from American and international standards for descriptions of the test protocols and pass/fail criteria when applicable.
Examples of strength of materials testing applicable to IV bags as container closure devices are as follows:

- Testing for leakage or sweating after bag is filled with appropriate volume of drug or solution with identical viscosity and specific gravity.
- Tensile strength and percent elongation of IV bag material.
- Pull-apart force at bag seams.
- Burst strength of bag.
- Puncture strength/penetration force to pierce bag.
- Axial disconnection force at tubing/bag connector.
- Off-axial disconnection force at tubing/bag connector.
- Measurement of creep under static (dead weight) load test conditions with resulting check for leakage, tears in bag, etc.

MOST RECENT (SUBJECT) SUBMISSION
Fresenius Kabi USA, LLC submitted their responses, dated 1/15/15, to all the deficiencies including engineering-related issues. Below are the responses to my deficiencies:

Responses to the information requests (Devices) received via email dated 15 December 2014 for Smoflipid NDA 207648.

FDA Comment: Clearly cite the container closure device/system for your drug product and include pictures, engineering drawings/schematics, etc.

FK Response:
The container closure system used for Smoflipid 20% is a single chamber flexible plastic IV bag known as packaging concept developed by Fresenius Kabi. Complete description including pictures and drawings are included in Section 3.2.P.7.1 of the original submission (SEQ 0000).

FDA Comment: In your submission you cited both three chamber and one chamber reservoir/IV bags as your container closure device.

FK Response:
We clarify that only single chamber IV bags were used as container closure system for Smoflipid 20% in the current NDA 207648.

FDA Comment: In addition, Provide all processing and bench testing to which your final finished device was subjected including all strength
of material testing. The description of the strength and material testing should include the test name, test pre-conditions and actual test conditions, the test protocol, the names of all apparatus employed in the testing along with last dates of calibration, past/fail criteria, and test results. You may substitute specifications from American and international standards for descriptions of the test protocols and pass/fail criteria when applicable. Examples of strength of materials testing applicable to IV bags as container closure devices are as follows:

- Testing for leakage or sweating after bag is filled with appropriate volume of drug or solution with identical viscosity and specific gravity.
- Tensile strength and percent elongation of IV bag material.
- Pull-apart force at bag seams.
- Burst strength of bag.
- Puncture strength/penetration force to pierce bag.
- Axial disconnection force at tubing/bag connector.
- Off-axial disconnection force at tubing/bag connector.
- Measurement of creep under static (dead weight) load test conditions with resulting check for leakage, tears in bag, etc.

FK Response:
The container closure system is tested according to the international standard ISO 15747 Plastic containers for intravenous injections and rubber stoppers are tested according to Ph. Eur. 3.2.9, equal to USP <381> for all physical and mechanical properties applicable to IV container/closure systems. A summary of all the tests performed for container closure system along with the methods/standards used, and acceptance criteria are provided in Table 4 below.

Table 5 has a list of instruments used for these tests together with the calibration dates during the test period (2010-2012).

Most of the example tests cited by FDA are covered under the tests performed by Fresenius Kabi for the packaging concept. A rationale is presented in Table 6.
Details of all these physical/mechanical tests performed including test conditions and/or standards used, number of batches tested, acceptance criteria and test results are described in the reports listed below, provided in the original submission. Wherever a standard method/test is not used, a short description of the method is included.

- Test Report on physical Suitability of the one chamber bag (Section 3.2.P.7.3 – SEQ 0000)
- Test Report on the general suitability and stability of the packaging concept (Section 3.2.P.7.4 – SEQ 0000).

The mechanical properties tested during the shelf life are described in Test Report on the general suitability and stability of the packaging concept (Section 3.2.P.7.4 – SEQ 0000). These tests show that
the tensile strength remains unaffected during the entire 24 months shelf life of the product. In the same document the tested during shelf life is also described. This test proves

Table 6  Rationale for Testing Applicable to IV Container Closure Systems

<table>
<thead>
<tr>
<th>Example tests applicable to IV container closure systems</th>
<th>Fresenius Kabi rationale for testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing for leakage or sweating after bag is filled with appropriate volume of drug or solution with identical viscosity and specific gravity.</td>
<td>Tensile strength is tested throughout the shelf life of the product (lipid emulsions). Parameters relevant to percent elongation are included in the tests - Resistance to temperature, pressure and leakage; and Resistance to dropping. Any relevant deformations due to high percent elongation or brittleness due to low percent elongation, to the bags would be observed during these tests.</td>
</tr>
<tr>
<td>Tensile strength and percent elongation of IV bag material</td>
<td>This test is performed and approved</td>
</tr>
<tr>
<td>Pull-apart force at bag seams.</td>
<td>Test method: Instron universal material testing system.</td>
</tr>
<tr>
<td>Burst strength of bag.</td>
<td>Although the burst strength of the bag is not measured, the strength of the filled bag is tested during the other tests - Resistance to temperature, pressure and leakage; and Resistance to dropping.</td>
</tr>
<tr>
<td>Puncture strength/penetration force to pierce bag.</td>
<td>The infusion port is tested for penetration force in the test “Access port” and the penetration force of the additive port is tested in Penetrability (needle).</td>
</tr>
<tr>
<td>Axial disconnection force at tubing/bag connector.</td>
<td>The infusion port is tested for the adhesion strength of the infusion device and impermeability. Disconnection force is not applicable as the IV infusion tubing is not to be disconnected from the bag during or after use.</td>
</tr>
<tr>
<td>Off-axial disconnection force at tubing/bag connector</td>
<td></td>
</tr>
<tr>
<td>Measurement of creep under static (dead weight) load test conditions with resulting check for leakage, tears in bag, etc.</td>
<td>Covered under the tests - Resistance to temperature, pressure and leakage; and Resistance to dropping</td>
</tr>
</tbody>
</table>

RECOMMENDATION
The responses to my deficiencies are acceptable. There are no outstanding engineering-related issues for the subject NDA.
<table>
<thead>
<tr>
<th>Role</th>
<th>Signature Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewer Sign-Off</td>
<td>William M. Burdick</td>
</tr>
<tr>
<td>Team Leader</td>
<td>Alan M. Stevens</td>
</tr>
<tr>
<td>Branch Chief Sign-Off</td>
<td>Richard Chapman</td>
</tr>
</tbody>
</table>

Reference ID: 3710039
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/s/

MATTHEW B BRANCAZIO
03/02/2015
Administratively entered for CDRH reviewer William Burdick.
REGULATORY PROJECT MANAGER
PHYSICIAN’S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: NDA 207648

Application Type: New NDA

Name of Drug/Dosage Form: SMOFLIPID 20% Lipid Injection Emulsion
Applicant: FRESENIUS KABI USA LLC

Receipt Date: 9/26/2014

Goal Date: 7/26/15

1. Regulatory History and Applicant’s Main Proposals
SMOFLIPID is indicated for use in the treatment of severe hypertriglyceridemia. SMOFLIPID, similar to other lipid injectable emulsions manufactured by Fresenius Kabi, is filled in flexible container/closure system. The packaging concept and its components used for SMOFLIPID

2. Review of the Prescribing Information
This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” checklist (see the Appendix).

3. Conclusions/Recommendations
SMOFLIPID format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SMOFLIPID format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 30, 2014. The resubmitted PI will be used for further labeling review.
Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be bolded and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

<table>
<thead>
<tr>
<th>Section</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>• Highlights Limitation Statement</td>
<td>Required</td>
</tr>
<tr>
<td>• Product Title</td>
<td>Required</td>
</tr>
<tr>
<td>• Initial U.S. Approval</td>
<td>Required</td>
</tr>
</tbody>
</table>
Selected Requirements of Prescribing Information

- Boxed Warning | Required if a BOXED WARNING is in the FPI
- Recent Major Changes | Required for only certain changes to PI*
- Indications and Usage | Required
- Dosage and Administration | Required
- Dosage Forms and Strengths | Required
- Contraindications | Required (if no contraindications must state “None.”)
- Warnings and Precautions | Not required by regulation, but should be present
- Adverse Reactions | Required
- Drug Interactions | Optional
- Use in Specific Populations | Optional
- Patient Counseling Information Statement | Required
- Revision Date | Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “HIGHLIGHTS OF PRESCRIBING INFORMATION”.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “Initial U.S. Approval:” followed by the 4-digit year.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word “WARNING” (even if more than one warning, the term, “WARNING” and not “WARNINGS” should be used) and other words to identify the subject of the warning (e.g., “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”). The BW heading should be centered.
Selected Requirements of Prescribing Information

Comment:
N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:
N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:
N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:
N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

N/A 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES
21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim bolded statement must be present: “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch”.

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three bolded verbatim statements that is most applicable:

If a product does not have FDA-approved patient labeling:

• “See 17 for PATIENT COUNSELING INFORMATION”

If a product has FDA-approved patient labeling:

• “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”
• “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be bolded and right justified (e.g., “Revised: 9/2013”).

Comment:
Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.
   
   Comment:

YES 26. The following heading must appear at the beginning of the TOC: “FULL PRESCRIBING INFORMATION: CONTENTS”. This heading should be in all UPPER CASE letters and **bolded**.
   
   Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
   
   Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
   
   Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
   
   Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
   
   Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
   
   Comment:
**Selected Requirements of Prescribing Information**

**Full Prescribing Information (FPI)**

**FULL PRESCRIBING INFORMATION: GENERAL FORMAT**

<table>
<thead>
<tr>
<th>BOXED WARNING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>3 DOSAGE FORMS AND STRENGTHS</td>
</tr>
<tr>
<td>4 CONTRAINDICATIONS</td>
</tr>
<tr>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td>6 ADVERSE REACTIONS</td>
</tr>
<tr>
<td>7 DRUG INTERACTIONS</td>
</tr>
<tr>
<td>8 USE IN SPECIFIC POPULATIONS</td>
</tr>
<tr>
<td>8.1 Pregnancy</td>
</tr>
<tr>
<td>8.2 Labor and Delivery</td>
</tr>
<tr>
<td>8.3 Nursing Mothers</td>
</tr>
<tr>
<td>8.4 Pediatric Use</td>
</tr>
<tr>
<td>8.5 Geriatric Use</td>
</tr>
<tr>
<td>9 DRUG ABUSE AND DEPENDENCE</td>
</tr>
<tr>
<td>9.1 Controlled Substance</td>
</tr>
<tr>
<td>9.2 Abuse</td>
</tr>
<tr>
<td>9.3 Dependence</td>
</tr>
<tr>
<td>10 OVERDOSAGE</td>
</tr>
<tr>
<td>11 DESCRIPTION</td>
</tr>
<tr>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>12.1 Mechanism of Action</td>
</tr>
<tr>
<td>12.2 Pharmacodynamics</td>
</tr>
<tr>
<td>12.3 Pharmacokinetics</td>
</tr>
<tr>
<td>12.4 Microbiology (by guidance)</td>
</tr>
<tr>
<td>12.5 Pharmacogenomics (by guidance)</td>
</tr>
<tr>
<td>13 NONCLINICAL TOXICOLOGY</td>
</tr>
<tr>
<td>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
</tr>
<tr>
<td>13.2 Animal Toxicology and/or Pharmacology</td>
</tr>
<tr>
<td>14 CLINICAL STUDIES</td>
</tr>
<tr>
<td>15 REFERENCES</td>
</tr>
<tr>
<td>16 HOW SUPPLIED/STORAGE AND HANDLING</td>
</tr>
<tr>
<td>17 PATIENT COUNSELING INFORMATION</td>
</tr>
</tbody>
</table>

**Comment:**

33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)].”
Selected Requirements of Prescribing Information

Comment: See inadvertently capitalized throughout the document. Please conform those items to match with the following; [see Warnings and Precautions (5.2)]

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: “FULL PRESCRIBING INFORMATION”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word “WARNING” (even if more than one Warning, the term, “WARNING” and not “WARNINGS” should be used) and other words to identify the subject of the Warning (e.g., “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”).

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

NO 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: Please add the verbatim statement to Post-Marketing Experience. "The following adverse reactions have been identified during post-approval use of (insert drug name). Because
Selected Requirements of Prescribing Information

these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:
Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME] (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

• [text]
• [text]

RECENT MAJOR CHANGES
[section (X.Y)] [m/year]
[section (X.Y)] [m/year]

INDICATIONS AND USAGE
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION
• [text]
• [text]

DOSAGE FORMS AND STRENGTHS
[text]

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
   2.1 [text]
   2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
   5.1 [text]
   5.2 [text]
6 ADVERSE REACTIONS
   6.1 [text]
   6.2 [text]
7 DRUG INTERACTIONS
   7.1 [text]
   7.2 [text]
8 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Labor and Delivery
   8.3 Nursing Mothers
   8.4 Pediatric Use
   8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
   9.1 Controlled Substance
   9.2 Abuse
   9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics
   12.4 Microbiology
   12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
   14.1 [text]
   14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW B BRANCAZIO
12/08/2014
LABEL AND LABELING AND HUMAN FACTORS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public ***

Date of This Review: December 8, 2014
Requesting Office or Division: Division of Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number: NDA 207648
Product Name and Strength: Smoflipid (Lipid Injectable Emulsion)
Lipid Injectable Emulsion for Intravenous Infusion, 20%
Product Type: Multiple Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Fresenius Kabi USA, LLC
Submission Date: September 25, 2014
OSE RCM #: 2014-2102 and 2014-2104
DMEPA Primary Reviewer: Sherly Abraham, R.Ph
DMEPA Team Leader: Kendra Worthy, Pharm.D.
DMEPA Associate Director: Lubna Merchant, M.S., Pharm.D.
1  REASON FOR REVIEW

This review responds to a request from DGIEP to evaluate the proposed prescribing information, and container labels, for areas of vulnerability that could lead to medication errors. This review also evaluates the use-related risk assessment study and the rationale that usability testing is not needed for this product submitted by Fresenius Kabi with their NDA as requested by the agency at the pre-NDA meeting on April 9, 2014.

2  MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)</td>
<td>B-N/A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>C</td>
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<tr>
<td>Human Factors Study</td>
<td>D-N/A</td>
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<tr>
<td>ISMP Newsletters</td>
<td>E-N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review

3  OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Fresenius Kabi USA, LLC submitted a 505 (b)(1) NDA to obtain a marketing approval of Smoflipid 20% in the United States. We reviewed the proposed prescribing information and container labels and identified areas in the label and labeling that can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

Of note, we are recommending a dual expression of strength for this drug product. Traditionally, the percentage strength (20 %) has been the sole strength expression on the label and labeling for lipid products. The advantages of maintaining this tradition include the healthcare practitioners’ (i.e., physicians, nurses, and pharmacists) familiarity with the use of percentages for selecting, prescribing, and administering lipid emulsion products and to maintain consistency in the strength presentation between other lipid products.
However, the current standard (for labels and labeling in general) is to include the total drug content in total grams per total volume (e.g., 20 grams/100 mL) followed by the number of grams per milliliter in accordance with USP General Chapter <1> requirements. This updated version of the strength statement is supported by the current recommendations for dosing and administration of this product which is stated as ‘XX grams/kg’. Hence, the pharmacist may refer to the total drug content to calculate the appropriate volume of lipid to add to the admixture and may be less prone to calculation errors and the presence of the percentage sign may confirm their selection of the proper strength. See our recommendations below in section 4.

Frenius Kabi submitted a risk assessment analysis conducted by [redacted] on Smoflipid [redacted] IV bags. [redacted] found users attempting to spike the additive port as one of the most likely failures with potential for patient harm. However, their expert panel provided the following risk mitigation strategies to minimize the risk:

- Additive port on the [redacted] IV bag would not accommodate a spike set.
- Usability testing of Fresenius Kabi three chamber bags with a similar port system demonstrated that users understood the port differentiation and no one attempted to spike the additive port.
- Modify warning statement on the additive port to discourage users from using this port.
- Replace [redacted] with a permanently sealed covering to create a port that cannot be accessed (i.e., blind port).

[redacted] concluded that the Smoflipid in the [redacted] IV bag is not different from currently available intravenous lipid emulsions and usability testing would not uncover additional risks. Additionally, independent heuristic analysis conducted by [redacted] also concluded that Smoflipid in [redacted] IV bag is approximately equivalent to other IV products. We also reviewed the pharmaceutical risk assessment study submitted with this NDA and agree with [redacted] and [redacted] conclusion that usability testing is not warranted for this product since administration of this product would not introduce any new risks or vulnerabilities.

4 CONCLUSION & RECOMMENDATIONS
DMEPA concurs with the Applicant that a Human Factors study is not warranted; however, the proposed prescribing information, label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.
4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information:

1. Consider replacing the symbols “<” and “>” in the dosage and administration section in the highlights and full prescribing information with their intended meanings to prevent misinterpretation and confusion.

2. Revise the presentation of the proprietary name from mixed case presentation “SMOFlipid” to titlecase “Smoflipid”. The mixed case presentation is typically reserved for differentiating look-alike names that have been confused in the marketplace. Since Smoflipid is not a name that has been involved in drug name confusion or wrong drug errors, the letters “SMOF” in the proposed proprietary name should not be capitalized.

4.2 RECOMMENDATIONS FOR THE FRESENIUS KABI USA, LLC

Based on this review, we recommend the following be implemented prior to approval of this NDA:

A. Container Labels:

1. Revise the presentation of the proprietary name from mixed case presentation “SMOFlipid” to titlecase “Smoflipid”. The mixed case presentation is typically reserved for differentiating look-alike names that have been confused in the marketplace. Since Smoflipid is not a name that has been involved in drug name confusion or wrong drug errors, the letters “SMOF” in your proposed proprietary name should not be capitalized.

2. Revise the strength presentation to add the total drug content in total grams per total volume followed by the number of grams per milliliter in accordance with USP General Chapter <1> requirements. For example,

   Smoflipid
   (Lipid Injectable Emulsion, USP) 20%
   20 grams/100 mL (0.2 gram/mL)

3. As currently presented, net quantity statement competes with the strength of the product for prominence. Relocate the net quantity statement away from the product strength to either below the route of administration (intravenous use) or on the upper right hand corner. Decrease the prominence of the net quantity statement by decreasing the font size.
4. Revise the statement, (b)(4) to “Protect from freezing”. Given the nursing standard of practice for changing IV tubing every 24 hours and that a patient is not likely to use 1000 mL of Smoflipid in a 24 hour period, consider adding the following statement: “Do not use beyond 24 hours once opened; discard unused portion after 24 hours.” Locate these statements after the storage statement on the principal display panel.

5. NDC numbers on all three package sizes are the same. NDC numbers are often used as an additional verification prior to drug dispensing in the pharmacy. Consider changing the last two digits of the NDC numbers to differentiate the package sizes.

6. Delete the following statements from the principal display panel to decrease clutter. These statements already appear in the strength presentation or insert labeling:
   a. (b)(4)
   b. Energy: 200 kcal per 100 mL
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION
Table 2 presents relevant product information for Smoflipid that Fresenius Kabi USA, LLC submitted on September 25, 2014.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Smoflipid</th>
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<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
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<tr>
<td><strong>Active Ingredient</strong></td>
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<td><strong>Indication</strong></td>
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<td><strong>Route of Administration</strong></td>
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<td><strong>Dosage Form</strong></td>
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<td><strong>Strength</strong></td>
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<td><strong>Dose and Frequency</strong></td>
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<td><strong>How Supplied</strong></td>
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<tr>
<td><strong>Storage</strong></td>
</tr>
<tr>
<td><strong>Container Closure</strong></td>
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</tbody>
</table>
APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods
We searched the L drive on November 10, 2014, using the terms, "lipid emulsion" to identify reviews previously performed by DMEPA.

C.2 Results
Our search identified one previous review\(^1\), a Human Factors Assessment memo.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed
Using the principles of human factors and Failure Mode and Effects Analysis,\(^2\) along with postmarket medication error data, we reviewed the following Smoflipid labels and labeling submitted by Fresenius Kabi USA, LLC submitted on September 25, 2014.

- Container label

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

/s/

SHERLY ABRAHAM
12/08/2014

KENDRA C WORTHY
12/08/2014

LUBNA A MERCHANT
12/08/2014

Reference ID: 3669093