CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207648Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 207648  SUPPL #  HFD #

Trade Name   SMOFLIPID (lipid injectable emulsion)

Generic Name   Soybean oil, USP/Medium Chain Triglycerides, NF/Olive oil, NF/Fish Oil, USP.

Applicant Name   Fresenius Kabi USA, LLC

Approval Date, If Known   July 13, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  YES ☒  NO ☐

   If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

   505(b)(1)

   b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety?  (If it required review only of bioavailability or bioequivalence data, answer "no.")

      YES ☒  NO ☐

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
c) Did the applicant request exclusivity? 

YES ☑ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☑

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☑

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II  FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES  
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☑

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020248  Intralipid 20% (soybean oil)

Smoflipid is a fixed-combination containing at least one drug substance, no active moiety of which has been approved in any other application under section 505(b) of the FD&C Act. As described in the Agency’s Guidance for Industry, New Chemical Entity Exclusivity for Certain Fixed-Combination Drug Products (2014), a drug substance is eligible for 5-year exclusivity, provided it meets the regulatory definition of new chemical entity, regardless of whether that drug substance is approved in a single-ingredient drug product or in a fixed-combination with another drug substance that contains no previously approved active moiety, or in a fixed-combination with another drug substance that contains a previously approved active moiety. Part III of this Summary will, thus, not be filled.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES □   NO □

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

      YES □   NO □

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

      YES □   NO □

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

      YES □   NO □

If yes, explain:
(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES □    NO □

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

   a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1       YES □    NO □
Investigation #2       YES □    NO □
Investigation #3       YES □    NO □

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:
b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>YES ☐ NO ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td>YES ☐ NO ☐</td>
</tr>
<tr>
<td>Investigation #3</td>
<td>YES ☐ NO ☐</td>
</tr>
</tbody>
</table>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

<table>
<thead>
<tr>
<th>Investigation #1, 2, &amp; 3</th>
<th>YES ☐ NO ☒</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND #</td>
<td>YES ☐ NO ☒</td>
</tr>
</tbody>
</table>

! Explain:
Investigations were performed in Belgium, France, Germany and Switzerland. Not under IND.
(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

<table>
<thead>
<tr>
<th>YES □</th>
<th>NO □</th>
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<tr>
<td>Explain:</td>
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Investigation #2

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Investigation #3

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<th>NO □</th>
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<tbody>
<tr>
<td>Explain:</td>
<td>Explain:</td>
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</table>

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

| YES □ | NO □ |

If yes, explain:
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELINE D LEEHOFFMAN
07/13/2016

JOYCE A KORVICK
07/13/2016
**ACTION PACKAGE CHECKLIST**

### APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>207648</th>
<th>NDA Supplement #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type:</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(an action package is not required for SE8 or SE9 supplements)</td>
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Proprietary Name: Smofiltrid 20%
Established/Proper Name: Lipid Injectable Emulsion, USP
Dosage Form: Emulsion, Injection

RPM: CPT. Kelly Richards, RN, MSN

Applicant: Fresenius Kabi USA, LLC
Agent for Applicant (if applicable):
Division: Gastroenterology and Inborn Errors Products

<table>
<thead>
<tr>
<th>NDA Application Type:</th>
<th>□ 505(b)(1)</th>
<th>□ 505(b)(2)</th>
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<td>Efficacy Supplement:</td>
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<table>
<thead>
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<th>□ 351(a)</th>
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<tbody>
<tr>
<td>Efficacy Supplement:</td>
<td>□ 351(k)</td>
<td>□ 351(a)</td>
</tr>
</tbody>
</table>

For ALL 505(b)(2) applications, two months prior to EVERY action:

- Review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)
  - No changes
  - New patent/exclusivity (notify CDER OND IO)
  Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

### Actions

- Proposed action
- User Fee Goal Date is October 26, 2015
- Previous actions (specify type and date for each action taken)

<table>
<thead>
<tr>
<th></th>
<th>□ AP</th>
<th>□ TA</th>
<th>□ CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
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</table>

If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?

Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ucm069965.pdf). If not submitted, explain

<p>| | |</p>
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<th></th>
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<tr>
<td>None</td>
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<tr>
<td>Received</td>
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</table>

### Application Characteristics

1. The Application Information Section is (only) a checklist. The Contents of Action Package Section (beginning on page 2) lists the documents to be included in the Action Package.

2. For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

3. Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Version: 8/13/15
Review priority: □ Standard □ Priority
Chemical classification (new NDAs only): 4
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

REMS:
☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)
  □ Yes □ No

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action
    □ Yes □ No
    - None
    - FDA Press Release
    - FDA Talk Paper
    - CDER Q&As
    - Other
  - Indicate what types (if any) of information were issued

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    □ No □ Yes
    - If so, specify the type

- Patent Information (NDAs only)
  - Patent Information:
    Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.
    □ Verified □ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List
- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)
  □ Included

Documentation of consent/non-consent by officers/employees
  □ Included
## Action Letters

- Copies of all action letters *(including approval letter with final labeling)*
  
  Action: 7/13/16 original-1

## Labeling

- **Package Insert** *(write submission/communication date at upper right of first page of PI)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    
    5/11/16
    
    □ Included 9/26/14
  - Original applicant-proposed labeling

- **Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling** *(write submission/communication date at upper right of first page of each piece)*
  - Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
  - Original applicant-proposed labeling

- **Labels** *(full color carton and immediate-container labels)* *(write submission/communication date on upper right of first page of each submission)*
  - Most-recent draft labeling
    
    □ Included 7/26/15

- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
    
    11/21/2014
    
    11/18/2014

- Labeling reviews *(indicate dates of reviews)*
  - RPM: □ None 3/17/15
    
    DMEPA: □ None 12/8/14
    
    DMPF/PLT (DRISK):
    
    □ None
    
    OPDP: □ None 6/29/15
    
    SEALD: □ None
    
    CSS: □ None
    
    Product Quality: □ None 12/8/14
    
    Other: □ None

## Administrative / Regulatory Documents

- **RPM Filing Review** *(indicate date of each review)*
  
  12/08/2014

- **All NDA 505(b)(2) Actions** *(date each action cleared by 505(b)(2) Clearance Committee)*
  
  □ Not a (b)(2)

- **NDAs only: Exclusivity Summary** *(signed by Division Director)*
  
  □ Included

- **Application Integrity Policy (AIP) Status and Related Documents**
  
  http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm

  - Applicant is on the AIP
    
    □ Yes □ No

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
• This application is on the AIP
  o If yes, Center Director’s Exception for Review memo (indicate date)
  o If yes, OC clearance for approval (indicate date of clearance
    communication)

☐ Yes ☒ No
☐ Not an AP action

❖ Pediatrics (approvals only)
  • Date reviewed by PeRC 10/14/15
  If PeRC review not necessary, explain:

❖ Breakthrough Therapy Designation
  • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)
  • CDER Medical Policy Council Breakthrough Therapy Designation
    Determination Review Template(s) (include only the completed template(s) and
    not the meeting minutes)
  • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy
    Designation for Recision Template(s) (include only the completed template(s)
    and not the meeting minutes)

(completed CDER MPC templates can be found in DARRTS as clinical reviews or on
the MPC SharePoint Site)

❖ Outgoing communications: letters, emails, and faxes considered important to include in
the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter,
Formal Dispute Resolution Request decisional letters, etc.) (do not include previous
action letters, as these are located elsewhere in package)

Ack Letter 10/06/2014
Filing Letter 12/04/2014
Review Extension 07/06/2015

❖ Internal documents: memoranda, telecons, emails, and other documents considered
important to include in the action package by the reviewing office/division (e.g.,
Regulatory Briefing minutes, Medical Policy Council meeting minutes)

❖ Minutes of Meetings
  • If not the first review cycle, any end-of-review meeting (indicate date of mtg)
  • Pre-NDA/BLA meeting (indicate date of mtg)
  • EOP2 meeting (indicate date of mtg)
  • Mid-cycle Communication (indicate date of mtg)
  • Late-cycle Meeting (indicate date of mtg)
  • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings)
    (indicate dates of mtgs)

☒ N/A or no mtg
☐ No mtg 4/19/14
☒ No mtg
☐ N/A 3/17/15
☐ N/A

❖ Advisory Committee Meeting(s)
  • Date(s) of Meeting(s)

☒ No AC meeting

Decisional and Summary Memos

❖ Office Director Decisional Memo (indicate date for each review)

☒ None

Division Director Summary Review (indicate date for each review)

☐ None 7/13/16

Cross-Discipline Team Leader Review (indicate date for each review)

☒ None

PMR/PMC Development Templates (indicate total number)

☐ None 8

Clinical

❖ Clinical Reviews
<table>
<thead>
<tr>
<th>Section</th>
<th>Review Status</th>
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<tbody>
<tr>
<td>Clinical Team Leader Review(s) <strong>(indicate date for each review)</strong></td>
<td>No separate review</td>
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<tr>
<td>Clinical review(s) <strong>(indicate date for each review)</strong></td>
<td>12/24/15</td>
</tr>
<tr>
<td>Social scientist review(s) <strong>(if OTC drug, indicate date for each review)</strong></td>
<td>None</td>
</tr>
<tr>
<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR</td>
<td>See Clinical Review, dated 12/24/15, page 33</td>
</tr>
<tr>
<td>If no financial disclosure information was required, check here and include a review/memo explaining why not <strong>(indicate date of review/memo)</strong></td>
<td></td>
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<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers <strong>(indicate date of each review)</strong></td>
<td>None</td>
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<tr>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation <strong>(indicate date of each review)</strong></td>
<td>N/A</td>
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<tr>
<td>Risk Management</td>
<td>N/A</td>
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<tr>
<td>- REMS Documents and REMS Supporting Document <strong>(indicate date(s) of submission)</strong></td>
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<tr>
<td>- REMS Memo(s) and letter(s) <strong>(indicate date(s))</strong></td>
<td>N/A</td>
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<td>- Risk management review(s) and recommendations (including those by OSE and CSS) <strong>(indicate date of each review and indicate location/date if incorporated into another review)</strong></td>
<td>None</td>
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<tr>
<td>OSI Clinical Inspection Review Summary(ies) <strong>(include copies of OSI letters to investigators)</strong></td>
<td>None requested 6/15/2015; 8/20/2015; 8/20/2015; 9/11/2015; 10/22/2015;</td>
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<tr>
<td>Clinical Microbiology</td>
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<td>Clinical Microbiology Review(s) <strong>(indicate date for each review)</strong></td>
<td>None 5/8/15</td>
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<td>Biostatistics</td>
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<td>Clinical Pharmacology</td>
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<td>None 6/10/2015</td>
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<td>OSI Clinical Pharmacology Inspection Review Summary <strong>(include copies of OSI letters)</strong></td>
<td>None requested</td>
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<td>Nonclinical</td>
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<td>Pharmacology/Toxicology Discipline Reviews</td>
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<td>• Supervisory Review(s) <em>(indicate date for each review)</em></td>
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<td>• Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
<td>☐ None 11/19/14, 6/30/15</td>
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<td>Statistical review(s) of carcinogenicity studies <em>(indicate date for each review)</em></td>
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<td>ECAC/CAC report/memo of meeting</td>
<td>☒ None Included in P/T review, page</td>
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<tr>
<td>OSI Nonclinical Inspection Review Summary <em>(include copies of OSI letters)</em></td>
<td>☒ None requested</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product Quality</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Quality Discipline Reviews</td>
<td></td>
</tr>
<tr>
<td>• Tertiary review <em>(indicate date for each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>• Secondary review <em>(e.g., Branch Chief)</em> <em>(indicate date for each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>• Integrated Quality Assessment <em>(contains the Executive Summary and the primary reviews from each product quality review discipline)</em> <em>(indicate date for each review)</em></td>
<td>☐ None 5/27/15, 10/6/15</td>
</tr>
<tr>
<td>Reviews by other disciplines/divisions/Centers requested by product quality review team <em>(indicate date of each review)</em></td>
<td>☐ None</td>
</tr>
<tr>
<td>Environmental Assessment <em>(check one)</em> <em>(original and supplemental applications)</em></td>
<td></td>
</tr>
<tr>
<td>☒ Categorical Exclusion <em>(indicate review date)</em> <em>(all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td>5/20/15 The claim of categorical exclusion is acceptable.</td>
</tr>
<tr>
<td>☐ Review &amp; FONSI <em>(indicate date of review)</em></td>
<td></td>
</tr>
<tr>
<td>☐ Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
<td></td>
</tr>
<tr>
<td>Facilities Review/Inspection</td>
<td></td>
</tr>
<tr>
<td>☒ Facilities inspections <em>(action must be taken prior to the re-evaluation date)</em> *(only original applications and efficacy supplements that require a manufacturing facility inspection <em>(e.g., new strength, manufacturing process, or manufacturing site change)</em></td>
<td>☒ Acceptable 6-28-16</td>
</tr>
<tr>
<td>Re-evaluation date:</td>
<td></td>
</tr>
<tr>
<td>☐ Withhold recommendation</td>
<td></td>
</tr>
<tr>
<td>☐ Not applicable</td>
<td></td>
</tr>
<tr>
<td>Day of Approval Activities</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td></td>
</tr>
<tr>
<td>▶ For all 505(b)(2) applications:</td>
<td></td>
</tr>
<tr>
<td>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
<td></td>
</tr>
<tr>
<td>▶ Finalize 505(b)(2) assessment</td>
<td></td>
</tr>
<tr>
<td>▶ For Breakthrough Therapy (BT) Designated drugs:</td>
<td></td>
</tr>
<tr>
<td>• Notify the CDER BT Program Manager</td>
<td></td>
</tr>
<tr>
<td>▶ For products that need to be added to the flush list (generally opioids): Flush List</td>
<td></td>
</tr>
<tr>
<td>• Notify the Division of Online Communications, Office of Communications</td>
<td></td>
</tr>
<tr>
<td>▶ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
<td></td>
</tr>
<tr>
<td>▶ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
<td></td>
</tr>
<tr>
<td>▶ Ensure that proprietary name, if any, and established name are listed in the <em>Application Product Names</em> section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
<td></td>
</tr>
<tr>
<td>▶ Ensure Pediatric Record is accurate</td>
<td></td>
</tr>
<tr>
<td>▶ Send approval email within one business day to CDER-APPROVALS</td>
<td></td>
</tr>
</tbody>
</table>
NDA 207648

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

Dear Ms. Rebbapragada:

Please refer to your New Drug Application (NDA) dated September 25, 2014, received September 26, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Smoflipid 20%, Lipid Injection Emulsion.

On June 29, 2015, we received your June 29, 2015, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 26, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 28, 2015.

If you have any questions, call CDR Matt Brancazio, Senior Regulatory Project Manager, at (301) 796-5343.

Sincerely,

Kevin Bugin, MS, RAC
Acting Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Reference ID: 3787978
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/s/

KEVIN B BUGIN
07/06/2015
MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 17, 2015

Application Number: NDA 207648
Product Name: Smoflipid 20%
Sponsor/Applicant Name: Fresenius Kabi USA, LTD

Subject: Midcycle Communication Meeting

FDA Participants
Joyce Korvick, M.D., MPH, Deputy Director of Safety, Division of Gastroenterology and Inborn Errors (DGIEP)
Ruiyi He, M.D., Medical Team Leader, DGIEP
Karyn Berry, M.D., Medical Review, DGIEP
Marie Kowblansky, Ph.D., CMC Team Leader,
Christina Capacci-Daniel, Ph.D., Office of Process and Facilities
CDR Matt Brancazio, Pharm.D., DGIEP

Sponsor/Applicant Participants
Philippe Moyen, Director, Project and Portfolio Management, Parenteral Nutrition
Patricia Anthony, MS, RD, Sr. Director, Medical Affairs, Clinical Nutrition
Jean-Marc Lohse, Clinical Project Manager, Clinical Studies & Medical Writing
Guenther Boos, Vice President, Global Clinical Quality Assurance & Safety and Global Regulatory Affairs
Lars Johnsson, Manager R&D Analytics, DC Parenteral Nutrition
Helena Skog, Quality Assurance, Plant Uppsala
Malin Abrahamsson, Director, Quality Assurance, Plant Uppsala
Aparna Dagar, PhD, RAC, Director, Regulatory Affairs
Karin Heindahl, Vice President, Regulatory Affairs, Parenteral Nutrition
Edward Tabor, MD, Vice President, Regulatory Affairs North America, Parenteral Nutrition
Lakshmi Rebbapragada, Supervisor, Regulatory Affairs

1.0 BACKGROUND:
Midcycle communication

Sponsor Teleconference information:
US: (040)
International: (040)
Conference code: (040)

2.0 DISCUSSION:

Office of Scientific Investigations
Discussion: Office is aware that FK is still coordinating inspection and material at the Grimm site. FK is in contact with the hospital and will coordinate with the Office of Regulatory Affairs.

Version: 03/05/2015

Reference ID: 3717225
FK stated that the inspection will occur at the site of the trial and that Dr. Grimm will travel with his own records to that inspection site.

**Office of Process and Facilities**
Inspections to support the review of this application are on-going. Please confirm with your drug substance and drug product manufacturing and testing facilities on their current status. A satisfactory evaluation of all facilities is required for NDA approval.

*Discussion:* FK is aware of the two drug substance inspections and that a response has been sent to the FDA for one site. FDA cannot comment further on the status.

**CMC:**
Answer the recent CMC IR as soon as possible.

*Discussion:* FK plans to submit the response by March 19, 2015.

**Clinical:**
*Provide the following data:*
- Triene/tetraene ratio (pre & post) for each patient (adults and pediatrics) by trial or identify where this can be found in the submission.
- Anthropometric measurements (pre & post) for each adult patient by trial (i.e. wt, ht., arm circumference)
- Percentage of enteral feedings that each patient received in the pediatric trials that allowed enteral nutrition

*Discussion:* Two of the three pediatric studies have the ratio and is available in the submitted documentation and FK will direct FDA to their locations in the submitted materials. FK will submit information to RPM in an email. For adults, ratios were not calculated per patient. FK will calculate a patient line list for the Hollman Index (pre and post ratio) for adults and submit to their NDA.

FK states that, for adults, they have body weight both pre and post treatment, but do not have a post-treatment height nor arm or waist circumference. FDA requests that FK identify if already in submission in table format, but if not, arrange the information in an easy-to-read table.

FK may have information related to the amount of fat calories provided by the enteral or oral feedings for each individual patient. Sponsor will provide this information once official IR has been issued.

**3.0 ACTION ITEMS:**
1. FK to send email to DGIEP RPM directing reviewers to information in the NDA.
2. DGIEP RPM to draft clinical IR post review of information from FK regarding location of clinical information above.
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
03/17/2015
Dear Ms. Rebbapragada:

Please refer to your New Drug Application (NDA) dated September 25, 2014, received September 26, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Smoflipid 20%, Lipid Injection Emulsion.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is July 26, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 28, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by January 15, 2015:

1. The draft package insert states that an admixture of the drug product with amino acids and dextrose may be held at 2-8°C and must be used within 24 hours following removal from refrigerated storage. Microbiological data should be provided to demonstrate that
the drug product solution will not support microbial growth during the proposed storage period. Provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the proposed storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Generally, "no growth" is interpreted as not more than a 0.5 log_{10} increase from the initial count; however, other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and an inoculum of low numbers (<100 CFU/mL) of challenge microbes. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature.

2. Your application describes container closure testing performed on the [ ] bags using a microbial ingress testing method. While your test method adequately demonstrates that the bag is capable of maintaining product sterility, it is unclear if your method is adequate to demonstrate that sterility is maintained throughout the entire fluid path of the container closure (including the injection and infusion ports). Provide additional information to support that container closure integrity is maintained through the entire fluid path of the drug product.

3. Your application states [ ] Your sterilization process validation information states that these studies were performed [ ] While it is acceptable for you to validate the sterilization process [ ] you must demonstrate that [ ] the drug product are appropriately qualified. Provide information from your three most recent qualification/requalification studies [ ] for drug product sterilization.

4. Your application alternately states that the maximum allowed [ ] bioburden is [ ] CFU/unit or ≤ [ ] CFU/100 mL (Control of Critical Steps and Intermediates section). Clarify the bioburden [ ] for your drug product.

5. Your application states that each drug product batch is subjected to a [ ] test. Provide more information on this test, including a description of test methods and test acceptance criteria.

6. In your Description of Manufacturing Process and Process Controls section, you state that drug product [ ] Clarify the sterilization parameters used for your drug product in production.

7. Your application describes [ ] studies to validate the sterilization cycle for your drug product. Address the following points:
   a. Clarify whether these studies were performed [ ]
b. State the justification studies. Provide a

c. State acceptance criteria for studies.
d. Describe positive controls used in these studies.
e. Describe the procedures used in these studies.

8. Provide the requalification schedule

9. Your application briefly describes a study

More information on this study is needed. Submit a description of test methods, acceptance criteria, and test results.

PREScribing INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified labeling issues and have labeling comments or questions as described in the attached labeling.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by December 22, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.
PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.
If you have any questions, call CDR Matthew Brancazio, Regulatory Project Manager, at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director of Safety
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD W ISHIHARA
12/04/2014
Signing for Joyce Korvick.

Reference ID: 3667803
Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

ATTENTION: Lakshmi Rebbapragada
Sr. Regulatory Specialist

Dear Ms. Rebbapragada:

Please refer to your New Drug Application (NDA) dated September 25, 2014, received September 26, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipid Injectable Emulsion, USP, for Intravenous Infusion, 20%.

We also refer to your correspondence requesting review of your proposed proprietary name, Smoflipid.

We have completed our review of the proposed proprietary name, Smoflipid and have concluded that it is acceptable. In addition, we have the following comments related to our review:

We note that you submitted your proposed proprietary name with the letters “SMOF” capitalized and the remainder of the name in lowercase letters. This mixed case presentation (tall man lettering) 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 in your labels and labeling.

If any of the proposed product characteristics as stated in your September 25, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Matthew Brancazio, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5343.

Sincerely,

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

/s/

KELLIE A TAYLOR
11/21/2014
NDA 207648

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

Dear Ms. Rebbapragada:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: SMOFlipid 20%

Date of Application: September 25, 2014

Date of Receipt: September 26, 2014

Our Reference Number: NDA 207648

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 25, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Reference ID: 3640101
The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastroenterology and Inborn Errors Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

[See appended electronic signature page]

CDR Matthew Brancazio, Pharm.D.  
Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research
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/s/

MATTHEW B BRANCAZIO
10/06/2014
PIND 102137

Fresenius Kabi USA, LLC
Attention: Aparna Dagar, PhD, RAC
Manager, Regulatory Affairs
Three Corporate Drive
Lake Zurich, Illinois 60047

Dear Dr. Dagar:

Please refer to your Pre-Investigational New Drug Application (PIND) file for SMOFlipid.

We also refer to the meeting between representatives of your firm and the FDA on April 9, 2014. The purpose of the meeting was to discuss with the Division the planned content of the New Drug Application for SMOFlipid.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Regulatory Project Manager at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

Matthew Brancazio, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 9, 2014, at 11:00 a.m. to 12:00 p.m.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: 102137
Product Name: SMOFlipid
Indication: 

Sponsor/Applicant Name: Fresenius Kabi

Meeting Chair: Ruyi He, M.D.
Meeting Recorder: LCDR Matthew Brancazio, Pharm.D.

FDA ATTENDEES
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Andrew E. Mulberg, M.D., F.A.A.P., Deputy Director, Division of Gastroenterology and Inborn Errors Products
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety, Division of Gastroenterology and Inborn Errors Products
Matthew Brancazio, Pharm.D., Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products
Ruyi He, M.D., Medical Team Leader, Division of Gastroenterology and Inborn Errors Products
Karyn Berry, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products
Marie Kowblansky, Ph.D., CMC Lead, Office of New Drug Quality Assessment
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, Division of Gastroenterology and Inborn Errors Products
Dinesh Gautam, Ph.D., Pharmacology Reviewer, Division of Gastroenterology and Inborn Errors Products
Jessica Kim, Ph.D., Statistical Reviewer, Division of Biometrics VII
Ling Lam, Ph.D., Statistical Reviewer, Division of Biometrics VII
Lubna Merchant, M.S., Pharm.D., Team Leader, Division of Medication Error and
Prevention Analysis
Matthew Barlow, R.N., Safety Evaluator, Division of Medication Error and Prevention Analysis
Susan Leibenhaut, M.D., Acting Team Leader, Division of Good Clinical Practice
Compliance
Wes Ishihara, Chief, Project Management Staff, Division of Gastroenterology and Inborn
Errors Products
Catherine Tran-Zwanetz, Regulatory Project Manager, Office of New Drug Quality Assessment
Quynh Nhu Nguyen, M.S., Biomedical Engineer, Office of Device Evaluation
Patricia Love, M.D., Deputy Director, Office of Combination Products
Bindi Nikhar, M.D., Acting Senior Clinical Advisor, Office of Combination Products
Donna Snyder, M.D., Medical Officer, Pediatric and Maternal Health Staff
Jennifer Sarchet, R.N., Regulatory Project Manager, Division of Gastroenterology and Inborn
Errors Products
Lening Shen, General Engineer, General Hospital Device Branch, Center for Devices and
Radiological Health

SPONSOR ATTENDEES (Fresenius Kabi)
Edward Tabor, Vice President, Regulatory Affairs North America
Pat Anthony, Senior Director, Medical Affairs
John Stover, Vice President, Medical Affairs
Philippe Moyen, Director, Project Management
Lars Johnsson, Manager, R&D Analytics
Norbert Breiter, Director, Preclinical Project Management
Astrid Spindler, Senior Manager, Scientific Affairs, Parenteral Nutrition
Jean-Marc Lohse, Clinical Project Manager
Karin Heimdahl, Vice President, Regulatory Affairs
Apama Dagar, Senior Manager, Regulatory Affairs

1.0 BACKGROUND
SMOFlipid by Fresenius Kabi is an intravenous lipid emulsion designed to provide energy and
essential fatty acids to patients receiving parenteral nutrition (TPN). It is a fixed physical mixture
of four different types of oils that are used worldwide in PN as lipid sources, namely soybean oil,
medium-chain triglycerides, olive oil, and fish oil. The proposed indication for SMOFlipid is as a

The sponsor requested this meeting to discuss with the Division the planned content of the New Drug
application for SMOFlipid. The Division of Gastroenterology and Inborn Errors Products
previously met with Fresenius Kabi on December 6, 2011, May 8, 2012, July 24, 2013, and
December 10, 2013 to discuss their pivotal study, endpoints to support NDA submission, format
for the electronic submission of the clinical study datasets, and proposed clinical and nonclinical
development plans.
2.0. DISCUSSION

2.1. Chemistry, Manufacturing, and Control

**Question 1:** Does the Division concur that the CMC information to be included at the time of submission is sufficient for filing the NDA?

**FDA Response to Question 1:**
The information you propose to submit is reasonable. However, we note that at the present time you do not plan to include testing for elemental impurities in the drug product specification, but will to do so when USP and ICH make their final recommendations regarding limits for these impurities. For this and similar products, FDA is currently requiring elemental impurity testing in the drug product specification. This should include testing for any other metals that are present during the manufacturing process and have the potential to contaminate the product. Acceptance criteria should be established on the basis of Permitted Daily Exposure (PDE), taking into consideration the maximum daily dose that is recommended for your product. While not yet finalized, PDEs recommended by ICH for parenteral products represent the best thinking on this subject at the present time. The daily exposure limits for manganese and zinc should be based on the reference dose (RfD) set by the US Environmental Protection Agency (EPA) for these metals.

The presence of heavy metals in PN can have significant adverse effects on organs and tissues, such as nephropathy, neurotoxicity and hepatotoxicity and nausea, vomiting and diarrhea.

Studies have demonstrated that trace elements are often present in significant concentrations in components of PN. The concentrations may vary markedly among solutions from different manufacturers and from different lots. Inadequate data concerning baseline levels of these heavy metals in PN products creates the potential for toxicity. Populations especially at risk for heavy metal toxicity include patients on long term PN use, pediatrics patients, renal and hepatic patients.

In addition, your submission should include a validated method for quantitating the following individual phytosterols in your product: include a commitment to test for these phytosterols in all batches of product manufactured over a three year period, and commit to submit a supplement establishing phytosterol specification limits at the end of the three year period.

**Meeting Discussion:**
FDA agrees to follow-up post meeting with information regarding the necessity of assay

**Post-meeting comments:**
Phytosterols have been implicated as a causative factor of parenteral nutrition associated liver disease. (Xu Z and Li Y-S, Hepatobiliary Pancreat Dis Int, Vol 11, No 6. December 15 2012). Phytosterols are an impurity present in Intravenous Fat Emulsion (IVFE) products and their presence is a potential safety issue. As a potential safety issue, there is a clinical need to assess/characterize the sterols.

**Question 2:** We request the Division’s confirmation that these stability data will be acceptable for filing the NDA and additional data for later time points may be submitted as they become available.

**FDA Response to Question 2:**
The stability data you intend to submit (as described in Table 8) should be acceptable for filing. However, you should be aware that we will not accept supplemental stability data any later than 30 days after the original NDA submission.

**Meeting Discussion:**
No further discussion required.

2.2. **Nonclinical**

**Question 3:** We request FDA’s concurrence that all nonclinical requirements have been met and the available nonclinical studies are sufficient to file the NDA.

**FDA Response to Question 3:**
Available nonclinical studies appear to be adequate to file the NDA. In addition, you will need to submit a complete toxicological evaluation of leachables and extractables from the packaging system in the NDA submission.

**Meeting Discussion:**
No further discussion required.

2.3. **Clinical**

**Question 4:** Does the Division agree with this proposed approach to address FDA’s request to evaluate a safety benefit for SMOFlipid?

**FDA Response to Question 4:**
Yes, your proposed approach to initiate your trial in parallel to the NDA seems reasonable. Based on review of your protocol synopsis, we have some remaining concerns about your study and suggest that you request a written response only meeting to discuss the final protocol.

**Meeting Discussion:**
FDA explains the additional concerns at this point are initially the inclusion of a background rate justification, including a hypothesis, written in a mathematical form to remove any ambiguity from decision on final result. In the detection of a potential safety signal, we would recommend a higher power in a clinical trial (i.e. 80% or more).
Further concerns may be raised during the review of the protocol during the type C written response only meeting request. The definition and rationale of the criterion (a) to be used for the safety definition need to be provided.

**Question 5:** At the Type C meeting in July 2013 the Division indicated that they would be looking at the outcome of the IVLE workshop with regard to their feedback on the study outline. Does the Division confirm that nothing in the IVLE workshop alters the recommendations provide at the Type C meeting.

**FDA Response to Question 5:**
In addition to recommendations provided at the July 2013 type C meeting, we also refer you to our February 2014 advice letter regarding recommendations for your Pediatric Study Plan.

Approval of your product will be based on a review of submitted data that demonstrates that it provides a source of calories and essential fatty acids in both acute and long term PN use.

We recommend nutritional efficacy in adult be assessed by at least the following parameters: body weight, arm circumference, skin-fold thickness, total protein, albumin, lipid metabolism (plasma triglycerides, total cholesterol, HDL cholesterol, phospholipids) and assessment for fatty acid deficiency. These data should be available from trials that exceed short-term (<2 weeks) exposure, and should include a control arm. Pediatric trials for intravenous fat emulsion products should be conducted to assess a signal of a serious risk of: essential fatty acid deficiency (short term and long term), sepsis, mortality and length of ICU/hospital stay (hospitalized patients), and risk of liver injury in pediatric patient including neonates.

**Meeting Discussion:**
Fresenius Kabi confirms that the indications for this NDA will include both adults and neonates. Fresenius Kabi also confirms that the requested endpoints would also be included in the planned studies. Approval for long-term or acute use would be decided based on the FDA review of the submitted data.

**3.0. Additional FDA Comments**

**A. Human Factors (HF)**

a) The submission does not include a systematic evaluation of use-related risk, a determination of the necessity of human factors validation and, if necessary, how you would undertake the human factors validation. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users.

b) This risk analysis of user tasks should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. You should also discuss risk-mitigation strategies you employed to
reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies.

c) Please provide a comprehensive analysis of use-related risks and a justification for whether an HF/usability validation study is necessary for the proposed product.

d) Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm. There is a more recent draft guidance document that includes the current thinking on human factors at CDRH and recommended approaches to human factors evaluation and testing: Applying Human Factors and Usability Engineering to Optimize Medical Device Design: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm

Meeting Discussion:
No further discussion required.

B. Manufacturing
a) Your proposed SMOFlipid® 20% Lipid Injectable Emulsion is a drug-device combination product and as such is subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at: https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products.

b) All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21 CFR Part 4 and the applicable 21 CFR Part 820 regulations should be submitted in Section 3.2.P.3. The list of manufacturing facilities provided on Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.

Meeting Discussion:
FDA confirms that this product would be subject to 21 CFR Part 4 and the applicable 21 CFR Part 820 regulations as described above and what would apply from these recommendations would be based on the manufacturing activities at the facility. FDA recommends that if Fresenius Kabi has specific requests regarding the requirements of the device component they should submit a separate meeting request.

C. Office of Scientific Investigations (OSI)
See attachment 1.
4.0. PREA REQUIREMENTS
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

5.0. PRESCRIBING INFORMATION
In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements of Prescribing Information website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

6.0. MANUFACTURING FACILITIES
To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation.
conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Corresponding names and titles of onsite contact:

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
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</tr>
</tbody>
</table>

7.0. 505(b)(2) REGULATORY PATHWAY
The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies...
described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

<table>
<thead>
<tr>
<th>Source of information (e.g., published literature, name of listed drug)</th>
<th>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Example: Published literature</td>
<td>Nonclinical toxicology</td>
</tr>
<tr>
<td>2. Example: NDA XXXXXX “TRADENAME”</td>
<td>Previous finding of effectiveness for indication X</td>
</tr>
</tbody>
</table>
### Example: NDA YYYYYY "TRADENAME"

| Previous finding of safety for Carcinogenicity, labeling section XXX |

| 4. |

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

**8.0. ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion,

**9.0. ATTACHMENTS AND HANDOUTS**

Please see OSI Appendix 1 and sponsor slides.
The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator’s site address or contact information since the time of the clinical investigator’s participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:

III. Request for Site Level Dataset:
Appendix 1

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

```
  ├── [m5]
  │    └── datasets
  │         └── bimo
  │             └── site-level
```

C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

Reference ID: 3490820
Appendix 1

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

15 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
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
04/16/2014