

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200656Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 200656

SUPPL #

HFD #

Trade Name Kabiven/PeriKabiven

Generic Name

Applicant Name Fresenius Kabi USA LLC

Approval Date, If Known August 25, 2014

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)(2)

c) 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:

d) Did the applicant request exclusivity?

YES NO

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

e) 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# 20678	Clinimix E sulfite free w/electrolytes in Dextrose with Calcium
NDA# 19683	Aminosyn II w/electrolytes in Dextrose with Calcium
NDA# 17957	Novamine 11.4% Injection
NDA# 18449	Intralipid 20%

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

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:

Kabiven Trials

PeriKabiven Trials

97-3CB1-001
98-3CB1-002
98-3CB1-003
00-3CB4-001
00-3CB5-001
01-3CB5-002
03-3CB7-001

98-3CB2-001
98-3CB2-002
98-3CB2-002
01-3CB6-001
03-3CB8-001

The bioequivalence study was used to establish efficacy. These studies were done by the sponsor and were used to support the safety.

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

Investigation #6	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #7	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #8	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #9	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #10	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #11	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #6	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #7	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #8	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #9	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #10	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #11	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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"):

Kabiven Trials

97-3CB1-001
 98-3CB1-002
 98-3CB1-003

PeriKabiven Trials

98-3CB2-001
 98-3CB2-002
 98-3CB2-002

00-3CB4-001
00-3CB5-001
01-3CB5-002
03-3CB7-001

01-3CB6-001
03-3CB8-001

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?
None of the above listed studies were not conducted under a US 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 !
!
YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

Investigation #2 !
!
YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

Investigation #3 !
!
YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the

study.

Investigation #4 !
!
YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

Investigation #5 !
!
YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

Investigation #6 !
!
YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

Investigation #7 !
!
YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

Investigation #8 !
!
YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

Investigation #9 !
!

YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

Investigation #10 !
! YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

Investigation #11 !
! YES ! NO
Explain: ! Explain:
The sponsor has certified that they provided substantial support for the study.

(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:

Name of person completing form: Matt Brancazio/Karyn Berry
Title: Regulatory Project Manager/Clinical Reviewer
Date:

Name of Office/Division Director signing form: Joyce Korvick

Title: ODEIII/DGIEP/Deputy Director for Safety

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

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
08/25/2014

JOYCE A KORVICK
08/25/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 200656 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Kabiven and PeriKabiven Established/Proper Name: Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose Dosage Form: Emulsion		Applicant: Fresenius Kabi USA, LLC Agent for Applicant (if applicable):
RPM: Matthew Brancazio		Division: Division of Gastroenterology and Inborn Errors Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	For ALL 505(b)(2) applications, two months prior to EVERY action: <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is 8/25/14 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input type="checkbox"/> None CR 11/21/11
❖ 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/Guidances/ucm069965.pdf). If not submitted, explain _____		
		<input type="checkbox"/> Received
❖ Application Characteristics³		

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, (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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

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: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No 8/5/14
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: 21 CFR 314.50(i)(1)(i)(A) Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 8/25/14 CR 11/21/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input checked="" type="checkbox"/> Included 08/22/14
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 1/28/11
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included 08/21/14
❖ Proprietary Name	Acceptability letter: 01/27/14; 11/20/11 Proprietary name review: 01/24/14; 11/10/11
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	
• Review(s) (<i>indicate date(s)</i>)	
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input checked="" type="checkbox"/> None 4/20/11 DMEPA: <input checked="" type="checkbox"/> None 4/14/14 DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> None 4/30/14 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	4/20/11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 4/14/14; 11/7/11
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included 08/25/14
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>Pediatric plan submitted 6/1/12</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	5/28/14; 5/22/14; 4/24/14; 4/24/14; 12/9/13; 11/4/11; 9/15/11; 9/08/11; 4/12/11; 3/01/11
<ul style="list-style-type: none"> ❖ 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) 	8/25/14; 8/19/14; 6/30/14; 5/22/14; 4/28/14; 7/20/11
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 7/20/09 <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> N/A <input type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 11/20/11
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 08/25/14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 08/14/14 ; 11/18/11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review 11/15/11; 03/25/11 <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	Clinical review (11/15/11), page 33
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	<input type="checkbox"/> None PMHS (5/22/14; 5/13/14; 9/26/11); OSE DMEPA (04/14/14)
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/5/14; 9/28/11; 3/24/11
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested 8/15/11
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 11/15/11
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 5/13/14; 11/21/11; 11/8/11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/13/14; 10/28/11; 3/8/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> No separate review 11/8/11
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 08/22/14; 6/11/14; 5/22/14; 11/8/11; 9/28/11; 3/24/11
❖ Microbiology Reviews		
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		<input type="checkbox"/> Not needed 9/21/11
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		
		<input type="checkbox"/> None CDRH (4/18/14; 12/6/13; 9/2/11)
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		9/28/11, page 80
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: 5/22/14 <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		
		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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/s/

MATTHEW B BRANCAZIO
08/25/2014

From: Lakshmi.Rebbapragada@fresenius-kabi.com
To: [Brancazio, Matthew \(FDA\)](mailto:Brancazio_Matthew_(FDA))
Subject: RE: NDA 200656 Kabiven/Perikabiven PMC
Date: Monday, August 25, 2014 4:17:16 PM

Matt,

We agree to this post marketing commitment and timelines.

Regards,
Lakshmi

From: "Brancazio, Matthew (FDA)" <Matthew.Brancazio@fda.hhs.gov>
To: "'Lakshmi.Rebbapragada@fresenius-kabi.com'" <Lakshmi.Rebbapragada@fresenius-kabi.com>,
Cc: "Brancazio, Matthew (FDA)" <Matthew.Brancazio@fda.hhs.gov>
Date: 08/25/2014 03:14 PM
Subject: RE: NDA 200656 Kabiven/Perikabiven PMC

Dear Lakshmi,

Please see the final proposed wording for the PMC with the agreed upon milestones captured during our discussion.

Conduct testing for (b) (4) content in the Kabiven or Perikabiven product. The testing will be divided into two phases:

1. Test batches of freshly manufactured product using six different batches of the (b) (4) bag.
2. Test six different batches of product at expiry.

Final Report Phase 1 : 03/16
Final Report Phase 2 : 12/18

Please respond with your concurrence in addition to the anticipated general correspondence to the NDA.

Respectfully,

Matt Brancazio, PharmD
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-5343 (office)
(301) 796-9904 (fax)
matthew.brancazio@fda.hhs.gov

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From: Lakshmi.Rebbapragada@fresenius-kabi.com [<mailto:Lakshmi.Rebbapragada@fresenius-kabi.com>]

Sent: Monday, August 25, 2014 4:10 PM
To: Brancazio, Matthew (FDA)
Subject: Re: NDA 200656 Kabiven/Perikabiven PMC

Matt,

Should I wait for you to send me revised PMC wording or should I cover the outcome of our conversation in my general correspondence letter?

I am waiting for your response.

Regards,
Lakshmi

From: "Brancazio, Matthew (FDA)" <Matthew.Brancazio@fda.hhs.gov>
To: "lakshmi.rebbapragada@fresenius-kabi.com" <lakshmi.rebbapragada@fresenius-kabi.com>,
Cc: "Bugin, Kevin" <Kevin.Bugin@fda.hhs.gov>, "Brancazio, Matthew (FDA)" <Matthew.Brancazio@fda.hhs.gov>
Date: 08/25/2014 01:02 PM
Subject: NDA 200656 Kabiven/Perikabiven PMC

Dear Lakshmi,

Please see the proposed Post Marketing Commitment for NDA 200656 that we want to add as a PMC.

We would like to discuss the timeline for the submission of the studies.

We request that you conduct testing for (b) (4) content in multiple batches of the Kabiven product. The testing should be conducted at expiry and include not only testing of multiple product batches, but multiple batches of the (b) (4) bag, as well. The results of these studies should be reported no later than xxx months.

Please contact the cc'd, Kevin Bugin, to coordinate the meeting.

Respectfully,

Matt Brancazio, PharmD
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-5343 (office)
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/s/

MATTHEW B BRANCAZIO
08/25/2014

MEMORANDUM

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

TELECON MEETING MINUTES

Meeting Date and Time: August 14, 2014 9:00 AM EST
Application Number: NDA 200656
Product Name: Kabiven/Perikabiven
Location: CDER WO 22 ROOM 5266
Indication: **Parenteral nutrition**

Meeting Chair: Ruyi He
Meeting Recorder: Matt Brancazio

FDA Attendees:

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., Team Leader, Office of New Drug Quality Assessment

Tarun Mehta, M.Sc., CMC Reviewer, Office of new Drug Quality Assessment

External Constituent Attendees (Fresenius Kabi):

Aparna Dagar, Ph.D, RAC, Director, Regulatory Affairs, Clinical Nutrition and Pharmaceuticals

Patricia Anthony, M.S., R.D. Head of Medical Affairs, Clinical Nutrition

Edward Tabor, M.D. Vice President, Regulatory Affairs North America Clinical Nutrition & Complex Formulations

Lakshmi Rebbapragada, M.Pharm, Sr. Regulatory Specialist, Clinical Nutrition and Pharmaceuticals

Karin Heimdahl, Vice President, Global Regulatory Affairs, Uppsala, Sweden

Mike Calsin, Director, Sales and Marketing

Caroline Strom, Manager, Customer Service and Material Management, Uppsala, Sweden

US: 1-877-326-2337

Conference code: (b) (4)

1. BACKGROUND:

2. DISCUSSION:

2.1. Administrative/Regulatory

1. (b) (4)

FK: FK will manufacture not more than (b) (4) units using the existing (b) (4). This could last (worst case) until (b) (4) by most likely by end of (b) (4). The new (b) (4) will be ordered, released, and installed providing product to the US within (b) (4).

FDA: We want (b) (4) only. If any product remains by end of (b) (4), it is to be discarded.

FK: FK agrees to request.

2. Product name

FK: The concern is the Amino Acids, Electrolytes, and Dextrose “in” the lipid emulsion. FK would request that we reconsider the previously requested name. It is 3 components in the bag, not 2 components suspended in lipid.

FDA: FDA explained that the thinking was that “when mixed” it is in an emulsion.

FK: FK is also concerned that the strength of the product should be in the name on the carton/container

FDA: We do not agree. It is the established name and the strength does not belong there. FDA inquires as to where FK will place the name if not in the proprietary name area.

FK: FK will need to review and respond.

For reference:

KABIVEN® (amino acids, electrolytes, and dextrose in lipid injectable emulsion), for intravenous use

With regard to your carton and container labels, please amend to the following:

1. Remove (b) (4)”
2. Add “No added sulfites” on a separate line below the Kabiven/PeriKabiven name

3. ACTION ITEMS:

3.1. Fresenius Kabi

Upon final decision of the name (see 3.2), FK will finalize the carton/container labels for submission and review.

3.2. FDA

FDA commits to explaining the rationale of FK to the workgroup again in the attempt to further understand the rationale of the name. This final decision will be communicated to FK as soon as possible.

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/s/

MATTHEW B BRANCAZIO
08/25/2014

From: [Brancazio, Matthew \(FDA\)](#)
To: lakshmi.rebbapragada@fresenius-kabi.com
Cc: [Brancazio, Matthew \(FDA\)](#)
Subject: NDA 200656 PeriKabiven label
Date: Tuesday, August 19, 2014 2:43:54 PM
Attachments: [NDA 200656 PeriKabiven clean 081914.doc](#)
[NDA 200656 PeriKabiven tracked 081914.pdf](#)
Importance: High

Dear Ms. Rebbapragada,

Please refer to your New Drug Application (NDA) dated January 28, 2011, received January 28, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Kabiven and PeriKabiven (lipid injectable emulsion with amino acids and electrolytes and dextrose). We further refer to the November 25, 2013, submission that constituted a complete response to our November 21, 2011, action letter.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, 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.

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

-
We request that you resubmit labeling that addresses these issues by August 21, 2014.

Respectfully,

Matt Brancazio, PharmD
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-5343 (office)
(301) 796-9904 (fax)
matthew.brancazio@fda.hhs.gov

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28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MATTHEW B BRANCAZIO
08/19/2014

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

BLA/NDA#: NDA 200656

PRODUCT PROPRIETARY NAME: Kabiven & Perikabiven **ESTABLISHED/GENERIC NAME:** Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose

APPLICANT/SPONSOR: Fresenius Kabi

PREVIOUSLY APPROVED INDICATION/S:

(1) _____

(2) _____

(3) _____

(4) _____

PROPOSED INDICATION/S:

Kabiven:

(b) (4)

Perikabiven

(b) (4)

BLA/NDA STAMP DATE: January 28, 2011

PDUFA GOAL DATE: August 25, 2014

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW *active ingredient(s) (includes new combination);* *indication(s);* *dosage form;* *dosing regimen;* or *route of administration?*

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes No

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes *No*

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes No

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.
- Pediatric Record

1. Pediatric age group(s) to be waived.
< 2 years of age
2. Reason(s) for waiving pediatric assessment requirements (**Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.**)
 - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
 - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
 - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (**This reason is for Partial Waivers Only**)

3. *Provide justification for Waiver:* The Division recommends a partial waiver for pediatric patient less than age 2 years. Kabiven and Perikabiven are new combination products that propose to provide parenteral nutrition (PN) in a three (3) chamber plastic bag. The individual chambers in Kabiven and Perikabiven contain: Glucose (b) % [Kabiven] and Glucose (b) % [Perikabiven] (Chamber 1); Amino acids (b) (4) including electrolytes (Chamber 2), and Intralipid 20% (Chamber 3). Nutritional needs vary based on the age and weight of the patient, so the sponsor calculated the nutrition requirements for each of the subgroups in the <2 year age group based on AAP and ASPEN recommendations. Based on these results, Kabiven and Perikabiven, which are fixed dose combinations, may not meet the nutritional needs of patients under 2 years of age.

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

The safety and effectiveness of KABIVEN in pediatric patients has not been established.

Deaths in preterm infants after infusion of intravenous lipid emulsion have been reported [See Warnings and Precautions (5.1)]. Patients, particularly preterm infants, are at risk for aluminum toxicity [See Warnings and Precautions (5.2)]. Hyperammonemia is of special significance in pediatric patients and may be related to urea cycle or genetic disorders [See Warnings and Precautions (5.3)]. Patients, including pediatric patients, may be at risk for PNALD [See 305 Warnings and Precautions (5.6)]. In clinical trials of a pure soybean oil based intravenous lipid emulsion product, thrombocytopenia in neonates occurred (<1%).

KABIVEN does not contain the amino acids cysteine and taurine, which are essential amino acids in neonates and young infants.

Newborns – especially those born premature and with low birth weight – are at increased risk of developing hypo – or hyperglycemia and therefore need close monitoring during treatment with intravenous glucose solutions to ensure adequate glycemic control in order to avoid

potential long term adverse effects. Hypoglycemia in the newborn can cause prolonged seizures, coma and brain damage. Hyperglycemia has been associated with intraventricular hemorrhage, late onset bacterial and fungal infection, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, prolonged length of hospital stay, and death. Plasma electrolyte concentrations should be closely monitored in the pediatric population as this population may have impaired ability to regulate fluids and electrolytes.

Perikabiven

The safety and effectiveness of Perikabiven® in pediatric patients has not been established.

Deaths in preterm infants after infusion of intravenous lipid emulsion have been reported [See *Warnings and Precautions (5.1)*]. Patients, particularly preterm infants, are at risk for aluminum toxicity [See *Warnings and Precautions (5.2)*]. Hyperammonemia is of special significance in pediatric patients and may be related to urea cycle or genetic disorders [See *Warnings and Precautions (5.3)*]. Patients, including pediatric patients, may be at risk for PNALD [See *305 Warnings and Precautions (5.6)*]. In clinical trials of a pure soybean oil based intravenous lipid emulsion product, thrombocytopenia in neonates occurred (<1%).

Perikabiven® does not contain the amino acids cysteine and taurine, which are essential amino acids in neonates and young infants.

Newborns – especially those born premature and with low birth weight – are at increased risk of developing hypo – or hyperglycemia and therefore need close monitoring during treatment with intravenous glucose solutions to ensure adequate glycemic control in order to avoid potential long term adverse effects. Hypoglycemia in the newborn can cause prolonged seizures, coma and brain damage. Hyperglycemia has been associated with intraventricular hemorrhage, late onset bacterial and fungal infection, retinopathy of prematurity, necrotizing enterocolitis,

bronchopulmonary dysplasia, prolonged length of hospital stay, and death. Plasma electrolyte concentrations should be closely monitored in the pediatric population as this population may have impaired ability to regulate fluids and electrolytes.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis	cancer (continued):
adjunctive treatment of major depressive disorder	follicular lymphoma
age-related macular degeneration	gastric
Alzheimer's disease	hairy cell leukemia
amyloidosis	hepatocellular
amyotrophic lateral sclerosis	indolent non-Hodgkin lymphoma
androgenic alopecia	lung (small & non-small cell)
atherosclerotic cardiovascular disease	multiple myeloma
autosomal dominant polycystic kidney disease (ADPKD)	oropharynx (squamous cell)
benign monoclonal gammopathy	ovarian (non-germ cell)
benign prostatic hyperplasia	pancreatic
cancer:	prostate
basal cell and squamous cell skin cancer	refractory advanced melanoma
bladder	renal cell
breast	uterine
cervical	chronic lymphocytic leukemia
colorectal	chronic obstructive pulmonary disease
endometrial	cryoglobulinemia
esophageal	diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

Pediatric Record

1. Age groups included in the deferral request: ages 2 to 16 years
2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:
The sponsor has requested a partial waiver for ages < 2 years
3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)*
 - a. Adult studies are completed and ready for approval
 - b. [REDACTED] (b) (4)
 - c. Other (specify)
4. Provide projected date for the submission of the pediatric assessment (deferral date): June 30, 2018
5. Did applicant provide certification of grounds for deferring assessments? Yes No
6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? Yes No
2. Does the division agree with the sponsor's plan? Yes No

3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? Yes No
- a. Protocol Submission: Expected date December 31, 2014
 - b. Study Completion: Expected date of completion: June 30, 2017
 - c. Study Submission: - June 30, 2018
4. Has a Written Request been issued? Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
5. Has a PPSR been submitted? Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design: Randomized, active comparator, open label trial to assess dosing and safety of Kabiven and Perikabiven in pediatric patients aged 2 to 16 years.

Nonclinical Studies: None

Clinical Studies: See above

Age group and population (indication) in which study will be performed:

Patients aged 2 to 16 years

This section should list the age group and population exactly as it is in the plan.

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:

Example:

Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:

This section should list pertinent inclusion/exclusion criteria:

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients must have a negative pregnancy test if female.

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments:

Example: baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed):

Example:

Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Division comments on product safety:

Are there any safety concerns currently being assessed? Yes No

Since the original review of NDA 200656, the Division has become aware of an unexpected serious risk of liver injury in pediatric and neonatal patients, which may be related to the presence of phytosterols. Phytosterols are impurities present in intravenous fat emulsion (IVFE) products and have been implicated as a causative factor of parenteral nutrition associated liver disease (PNALD). The Division considers this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA. (b) (4), (b) (5)

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? Yes No

Will a DSMB be required? Yes No

Other comments:

Division comments on product efficacy:

The individual components of Kabiven and Perikabiven have a long established history of clinical use for Parenteral Nutrition (PN) in the US. Irrespective of the underlying disease state, the primary purpose of PN is maintenance of an adequate nutritional state or its improvement in a previously undernourished individual when other forms of nutrition are inadequate or contraindicated. These are conditions that can occur in pediatric as well as adult patients. The purpose of total parenteral nutrition (TPN) is therefore to maintain or improve the patient's nutritional state when the gastrointestinal tract cannot or should not perform its normal digestive function.

Efficacy of Kabiven and Perikabiven in adults was assessed by clinical pharmacology studies and supportive clinical trials. The clinical trials included laboratory efficacy assessments such as essential and non-essential amino acids, fatty acid components, urea, creatine and pre-albumin. The sponsor proposes

(b) (4)
(b) (4)

Division comments on sponsor proposal to satisfy PREA:

The Division agrees that

(b) (4)

PeRC ASSESSMENT TEMPLATE

Please attach:

Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the

appropriate language at the end of this form.
 Pediatric Record

Date of PREA PMR:

Description of PREA PMR: *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC? Yes No If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

This section should list the indication(s) exactly as written in the *protocols*.

Example:

DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration:** *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:

Example:

Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.

Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:

Example:

Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients had a negative pregnancy test if female.

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed):

This section should list the statistical tests conducted.

Example:

Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, C/F and compared to adults.

Timing of assessments:

Example:

Baseline, week 2, week 6, and end of treatment

Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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/s/

MATTHEW B BRANCAZIO
08/19/2014

**PeRC PREA Subcommittee Meeting Minutes
June 18, 2014**

PeRC Members Attending:

Lynne Yao
Gregory Reaman
Hari Cheryl Sachs
George Greeley
Andrew Mosholder
Robert "Skip" Nelson
Daiva Shetty
Wiley Chambers
Susan McCune
Kevin Krudys
Gilbert Burckart
Rachel Witten
Andy Mosholder
Kristiana Brugger
Suresh Pagay
Tom Smith
Karen Davis Bruno
Adrienne Hornatko-Munoz ((b) (4) review only)

PREA

10:50	BLA	(b) (4)	(b) (4)	(b) (4)
11:10	NDA	200656	Kabiven Perikabiven (lipid injectable emulsion with amino acids and electrolytes and dextrose) Partial Waiver/Deferral/Plan	(b) (4) (See PeRC template)
	<i>NDA</i>	(b) (4)	(b) (4)	(b) (4)

(b) (4)

Kabiven Perikabiven Partial Waiver/Deferral/Plan

- NDA 200656 seeks review of Kabiven Perikabiven (b) (4) (lipid injectable emulsion with amino acids and electrolytes and dextrose) (b) (4)

(b) (4)

- The application has a PDUFA goal date of August 25, 2014.
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a partial waiver in patients in less than 2 years of age. The PeRC also recommends that Section 8.4 of the label be updated to include information on the limitations of use.
 - Some PeRC members recommended that the product be waived due to safety to be clear on the safe use in children while others agreed to the waiver because of it not offering a meaningful therapeutic benefit.
 - The Division clarified that PeriKabiven is the same as Kabiven except for a lower dextrose concentration to allow for peripheral administration. The PeRC agreed with the Division's plan to study Kabiven first because it is a centrally administered product. If there are no new safety or efficacy issues identified with Kabiven then the PeRC agrees that studies in Perikabiven would not be needed.

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/s/

GEORGE E GREELEY
06/30/2014

From: [Brancazio, Matthew \(FDA\)](#)
To: Aparna.Dagar@fresenius-kabi.com
Cc: lakshmi.rebbapragada@fresenius-kabi.com; [Brancazio, Matthew \(FDA\)](#)
Subject: NDA 200656 Kabiven/Perikabiven - Information Request
Date: Wednesday, May 28, 2014 8:50:58 AM
Importance: High

Good morning,

Please see the information request below based on the clinical sections of your submission:

*Your request for a partial waiver for pediatric patients less than 2 years of age may be appropriate on the grounds that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s). Before this determination can be made additional information is needed.*

Provide more information on why Kabiven and Perikabiven would not be appropriate for the pediatric population below age 2 years based on maintenance parental nutritional requirements established by AAP and ASPEN. You should perform nutritional calculations to determine the utility of the various components of these products in children less than 2 years of age at different patient weights to assess if patients will receive current acceptable and adequate ratios of amino acids, fat and dextrose. You should take into account how these products may be used in the clinical setting, i.e. use of cyclic infusion regimens in stable patients.

-
Please reply with this information by June 2, 2014, if not sooner.

Respectfully,

Matt Brancazio, PharmD
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-5343 (office)
(301) 796-9904 (fax)
matthew.brancazio@fda.hhs.gov

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/s/

MATTHEW B BRANCAZIO
05/28/2014

MEMORANDUM

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

TELECON MEETING MINUTES

Meeting Date and Time: May 22, 2014 10:30 AM EST
Application Number: NDA 200656
Product Name: Kabiven/Perikabiven
Location: CDER WO 22 ROOM 5201 10:30 AM EST
Indication: **Parenteral nutrition**

Meeting Chair: Joyce Korvick
Meeting Recorder: Matt Brancazio

FDA Attendees:

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Matthew Brancazio, Pharm.D., Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products
Joyce Korvick, M.D., M.P.H., Deputy Director of Safety, Division of Gastroenterology and Inborn Errors Products
Ruyi He, M.D., Medical Team leader, Division of Gastroenterology and Inborn Errors Products
Wes Ishihara, Chief, Project Management Staff, Division of Gastroenterology and Inborn Errors Products

External Constituent Attendees (Fresenius Kabi):

Edward Tabor, M.D., Vice President, Regulatory Affairs North America, Parenteral Nutrition
Lakshmi Rebbapragada, Senior Regulatory Specialist, Regulatory Affairs
Aparna Dagar, PhD, RAC, Director, Regulatory Affairs
Phillipe Moyen
Pat Anthony
???

Conference number: 1-877-326-2337
code: (b) (4)

1. BACKGROUND:

2. DISCUSSION:

2.1. Administrative/Regulatory

FDA states that the division will take a review extension based on the April 29, 2014, major

amendment. FDA will continue to work diligently with Fresenius Kabi for the labeling and PMR negotiations to bring the NDA to a swift resolution. The new PDUFA date is August 25, 2014.

Fresenius Kabi clarified the outstanding issues (i.e. labeling, Pediatric plan, and DMF)

3. ACTION ITEMS:

3.1. Fresenius Kabi

3.2. FDA

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/s/

MATTHEW B BRANCAZIO
05/22/2014



NDA 200656

**REVIEW EXTENSION –
MAJOR AMENDMENT**

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 January 28, 2011, received January 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kabiven and Perikabiven (lipid injectable emulsion with amino acids and electrolytes and dextrose).

We also refer to your November 25, 2013, submission containing a complete response to our November 21, 2011, action letter.

On April 29, 2014, we received your April 29, 2014, 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 August 25, 2014.

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 August 4, 2014.

If you have any questions, call Matthew Brancazio, Pharm.D., 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

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/s/

RICHARD W ISHIHARA
05/22/2014

MEMORANDUM

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

TELECON MEETING MINUTES

Meeting Date and Time: April 9, 2014 11:35 AM EST
Application Number: NDA 200656
Product Name: Kabiven/Perikabiven
Location: CDER WO 22 ROOM 1309 11:30am-12:00pm
Indication: **Parenteral nutrition**

Meeting Chair: Ruyi He
Meeting Recorder: Matt Brancazio

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
Patricia Love, M.D., Deputy Director, Office of Combination Products
Bindi Nikhar, M.D., [Associate Clinical Director, 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
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

External Constituent Attendees (Fresenius Kabi (FK)):

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
Aparna Dagar, Senior Manager, Regulatory Affairs

1. BACKGROUND:

Your proposed Kabiven and PeriKabiven (b) (4) 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>.

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.

2. DISCUSSION:

2.1. OCP

GMP rule Part 4 was finalized in Jan 2013 with implementation in July 2013. The proposed rule was published in 2009 (draft guidance in 2006). Since at least 2011 both CDER and FK letters identified the device component.

CDRH OC reviews the application information and identifies the facilities for device related inspection.

FDA cannot comment on ongoing inspections and cannot provide information based on the facility.

FK is concerned that a delay in inspections or the impact of device inspection would impact their NDA and the approvability.

FDA is aware of FK's concerns, but until the inspection is finished we cannot comment or move forward. FDA would need to see the specifics of the inspection report (not just the 483). Once we have the report and understand any identified issues we can determine what can be communicated. FDA commits to contacting FK to discuss how to overcome any issues.

FK requests if any deficiencies or gaps could be addresses post marketing. FDA cannot comment on specifics until the inspection has been completed (i.e. 483 and final written report).

3. ACTION ITEMS:

**3.1. Fresenius Kabi
No further actions required**

**3.2. FDA
Review the inspection material and contact with FK to address any gaps or deficiencies.**

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/s/

MATTHEW B BRANCAZIO
04/28/2014



NDA 200656

GENERAL ADVICE

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KABIVEN and PERIKABIVEN.

We also refer to your November 22, 2013, submission, containing a class 2 response to our November 21, 2011, action letter.

We are reviewing your application and have identified the following concerns:

Our field investigator could not complete an inspection of the (b) (4) manufacturing facility at (b) (4), because the facility was not ready for inspection. Satisfactory inspection is required before this application may be approved. You informed us that production of (b) (4) has been moved to the (b) (4) manufacturing facility at (b) (4). Please amend your application accordingly.

We are providing these comments to you before completing our review of your entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

JOYCE A KORVICK
04/24/2014

From: [Brancazio, Matthew \(FDA\)](#)
To: ["Aparna.Dagar@fresenius-kabi.com"](mailto:Aparna.Dagar@fresenius-kabi.com)
Cc: [Brancazio, Matthew \(FDA\)](#); lakshmi.rebbapragada@fresenius-kabi.com
Subject: NDA 200656 - PAI observation regarding combination products--discussion points
Date: Thursday, April 24, 2014 1:57:08 PM
Importance: High

Dear Aparna,

In your April 21, 2014, email you stated the following:

The requested teleconference is in reference to the observation the inspector provided for Kabiven and Perikabiven during the PAI held March 31- April 11 at Uppsala, Sweden (below):

"Failure to establish and maintain procedures to control the design of a device in order to ensure that specified design requirements are met. Specifically, procedures for design input, design output, design review, design verification, and design validation were not established for the device constituent part of the finished combination product Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose (Kabiven and (b) (4)) in the three chamber IV bag (pending NDA 200-656)."

Question: As this requirement was only recently communicated during the inspection, the creation, finalization and implementation (including training) of these procedures will take time and cannot be done within the NDA resubmission goal date of May 25, 2014.

We have already demonstrated product development and optimization steps taken for Kabiven and Perikabiven in 3-chamber bags and performed validation studies to confirm the design meets user needs enabling them to use the product safely and effectively. We want to discuss the impact of the requested procedural requirements and planned steps for implementation on the NDA review, if any and also discuss how we can agree on timelines for this implementation so that this additional requirements do not delay the NDA approval goal date.

We have prepared a response to your question in lieu of a teleconference at this time to allow for preparation of the material prior to your designated response date. We are not refusing a teleconference at this time, but feel the following statements below could suffice. Regarding applicability of 21 CFR Part 4, we reference the notice and comment rule making from 2009 to the final rule of January 2013.

You indicated that under 21 CFR 211 you had identified and validated user needs for the device constituent part. To demonstrate how you address this issue provide the documents to show the following:

- The user needs that firm identified for validation. This could be part of your design plan, a report, or part of a risk/hazard control plan.
- The plan the sponsor developed to validate those user needs
- The results of that validation activity.

In addition, submit the plan you have developed to prospectively address the establishment of procedures for design validation as indicated in the 483 Observation in question.

Respectfully,

Matt Brancazio, PharmD
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

CDER/FDA

(301) 796-5343 (office)

(301) 796-9904 (fax)

matthew.brancazio@fda.hhs.gov

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/s/

MATTHEW B BRANCAZIO
04/24/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 200656

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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) resubmission dated November 22, 2013, received November 25, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the central formulation of [REDACTED] (b) (4)

and also the central/peripheral formulation of [REDACTED] (b) (4)

We also refer to your November 22, 2013, correspondence, received November 25, 2013, requesting review of your proposed proprietary names, Kabiven (for the central formula), and Perikabiven (for the central/peripheral formula). We have completed our review of the proposed proprietary names, Kabiven and Perikabiven, and have concluded that these names are acceptable.

If **any** of the proposed product characteristics as stated in your November 22, 2013, 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 Phong Do, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. 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}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
01/27/2014



NDA 200656

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

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

Dear Ms. Rebbapragada:

We acknowledge receipt on November 25, 2013, of your November 22, 2013, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for KABIVEN and PERIKABIVEN.

We consider this a complete, class 2 response to our November 21, 2011, action letter. Therefore, the user fee goal date is May 25, 2014.

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

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/s/

MATTHEW B BRANCAZIO
12/09/2013



NDA 200656

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

APP Pharmaceuticals, LLC
1501 East Woodfield Road
Suite 300 East
Schaumburg, IL 60173

ATTENTION: Aparna Dagar, Ph.D.
 Supervisor, Regulatory Affairs

Dear Dr. Dagar:

Please refer to your New Drug Application (NDA) dated and received January 28, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the (b) (4)

[REDACTED]

[REDACTED] and also the central formulation of (b) (4)

[REDACTED]

We also refer to your correspondence, dated September 7, 2011, received September 8, 2011 requesting review of your proposed proprietary names, Kabiven (for the central formula), and Perikabiven (for the (b) (4) formula). We have completed our review of the proposed proprietary names and have concluded that the names are acceptable.

The proposed proprietary names, Kabiven and Perikabiven, will need to be re-reviewed upon resubmission of your NDA and 90 days prior to the approval of the NDA. If we find the names

unacceptable following the re-review, we will notify you. You should submit a letter in your resubmission stating you want us to review your names and provide us with the most current full set of labels

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact Maria R. Walsh, Office of New Drugs Regulatory Project Manager, at (301) 796-1017.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk

Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
11/22/2011

MEMORANDUM OF TELECON

DATE: November 4, 2011

APPLICATION: NDA 200656

PRODUCT NAME: Kabiven and (b) (4) (lipid injectable emulsion with amino acids and electrolytes and dextrose)

MEETING RECORDER: Maria R. Walsh

APP Pharmaceuticals

Malin Abrahamsson, Ph.D., Manager Product Maintenance, Fresenius Kabi, Uppsala, Sweden
Alexander Stoll, Ph.D., Director QA and Qualified Person, Fresenius Kabi, Uppsala, Sweden
Torbjörn Wärnheim, Ph.D., Associate Professor, Director I&DC Parenteral Nutrition, Fresenius Kabi, Sweden

Karin Heimdahl, Vice President Regulatory Affairs, Fresenius Kabi, Sweden

Aparna Dagar, Ph.D., Supervisor, Regulatory Affairs

FDA

Marie Kowblansky, Ph.D., CMC Lead, Division of New Drug Quality Assessment II

Maria R. Walsh, R.N., M.S., Associate Director for Regulatory Affairs, Office of Drug Evaluation III

SUBJECT: Particulate matter observed in ongoing stability studies

BACKGROUND: APP requested a teleconference with the chemistry team to discuss the November 2, 2011 amendment describing their ongoing stability program in which four of the nine pivotal batches showed results above the specification limit of particulate matter. APP has determined that the particles present in the lipid chamber of the IV bag are (b) (4) and are caused by migration of components from the stopper.

APP proposes the following corrective actions:

- Fresenius Kabi will implement a modified stopper to reduce the amount of (b) (4).
- New stability batches of Kabiven and (b) (4) using the newly identified stopper with reduced (b) (4) content will be manufactured and put on stability. Stability testing will be performed in accordance with the stability protocol used for the ongoing study with the addition that the particulate matter in the emulsion will be analyzed at each testing point.

APP proposes the following commitments re: shelf life:

- The target shelf life, aimed for in the pivotal stability studies, is 24 months when stored not above 25°C.
- Considering the documented mechanism for formation of (b) (4), Fresenius Kabi suggests to (b) (4)
- Not until corrective actions are implemented will shelf life will be reverted to 24 months.

DISCUSSION POINTS:

- FDA agreed that a (b) (4)-month expiration dating period would likely be appropriate, but only if APP conducts a refrigeration study. The study should be conducted with stability batches that contain relatively high levels of particulate matter but are still within specification limits. Also, the study should be conducted in the same manner as the refrigeration study that was conducted to support the recommendation for refrigerated storage in the proposed labeling. APP agreed to conduct the study and the results will be submitted in an amendment for FDA review.
- FDA agreed that shelf life may be extended to 24 months if the stability studies demonstrate conformance to all specification requirements over 24 months at the proposed storage conditions. FDA also recommended that the stoppers be tested for (b) (4) levels and limits for (b) (4) content be added to the stopper specification, once acceptable levels are established. APP said the supplier is using an optimized process to decrease the amount of (b) (4) in the stoppers and asked if it would be acceptable to provide a certificate of analysis (CoA) from the supplier for this purpose. FDA said this would be acceptable if APP includes the CoA in the NDA along with an explanation of how the process was optimized.

The call was then concluded.

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/s/

MARIE KOWBLANSKY
11/04/2011



NDA 200656

DEFICIENCIES PRECLUDE DISCUSSION

APP Pharmaceuticals, LLC.
Attention: Aparna Dagar, Ph.D.
Supervisor Regulatory Affairs
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Dr. Dagar:

Please refer to your January 28, 2011 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose.

We also refer to our April 12, 2011, letter in which we notified you of our target date of November 7, 2011 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, call Maria R. Walsh, Regulatory Project Manager, at (301) 796-1017.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., MBA
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
11/04/2011



NDA 200656

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

APP Pharmaceuticals, LLC
Attention: Aparna Dagar, PhD
Senior Regulatory Scientist
APP Pharmaceuticals, LLC
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kabiven and (b) (4).

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b) (4)¹. The pervasiveness and egregious nature of the violative practices by (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at (b) (4) from (b) (4), as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented (b) (4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b) (4) (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

¹ These violations include studies conducted by (b) (4) (b) (4)

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED] (b) (4) during the time period of concern ([REDACTED] (b) (4)). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Giuseppe Randazzo, M.S., Regulatory Scientist, at (301) 796-3277.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GIUSEPPE RANDAZZO

09/15/2011

Signed for Dr. Donna Griebel



NDA 200,656

PREA WAIVER DENIED

APP Pharmaceuticals, LLC
A Company of the Fresenius Kabi Group
Attention: Aparna Dagar, PhD.
Senior Regulatory Scientist
1501 East Woodfield Rd., Suite 300E
Schaumburg, IL 60173

Dear Dr. Dagar:

Please refer to your submission dated August 5, 2011 requesting (b) (4) (u) (4) for Kabiven and (b) (4) (u) (4) (lipid injectable emulsion with amino acids and electrolytes and dextrose), hereafter referred to as Kabiven and (b) (4).

We have reviewed your submission and do not agree (b) (4) is justified for Kabiven and (b) (4)

(b) (4)

(b) (4)

We are denying your request (b) (4) for the following reasons:

- (b) (4)
- (b) (4)

We will however consider a partial waiver of the pediatric study requirement for birth to 11 months (inclusive) as there are commercially available FDA-approved amino acid solutions designed for infants (<12 months of age) requiring parenteral nutrition. If you plan to seek a partial waiver for this age group, you must submit data to show that Kabiven and (b) (4) (b) (4) do not represent a meaningful benefit over existing therapies and are not likely to be used in a substantial number of pediatric patients in this age group.

Submit your pediatric plan within 30 days from the date of this letter. A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetic/pharmacodynamics, safety and efficacy) you plan to conduct. The pediatric plan must contain a timeline for the completion of these studies, i.e., the dates of (1) protocol submission, (2) study completion, and (3) submission of study reports. In addition, you must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

Please also note the following:

1. If you propose to (b) (4)
(b) (4)
2. (b) (4)
3. A 3-in-1 parenteral nutrition product containing an amino acid source designed for infants (<12 months of age) and Intralipid would likely represent a meaningful benefit over existing therapies.

We also refer you to the Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>.

Pediatric studies conducted under the terms of Section 505B of the Federal Food, Drug and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of Section 505A of the Act. If you wish to qualify for pediatric exclusivity, consult the Division of Gastroenterology and Inborn Errors Products. Please note that satisfaction of the requirements in Section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have questions, please call Frances Fahnbulleh, Regulatory Project Manager, at 301-796-0942.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
09/08/2011



NDA 200,656

FILING COMMUNICATION

APP Pharmaceuticals, LLC
Attention: Aparna Dagar, PhD.
Senior Regulatory Scientist
1501 East Woodfield Rd., Suite 300E
Schaumburg, IL 60173

Dear Dr. Dagar:

Please refer to your New Drug Application (NDA) dated and received on January 28, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Kabiven and [REDACTED] (b) (4).

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 November 28, 2011.

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, midcycle, 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 November 7, 2011.

During our filing review of your application, we identified the following potential review issues:

1. Proposed PLR labeling should include a DRUG INTERACTIONS Section 7.0. Include any observed or predicted drug-drug (prescription or OTC) or drug-laboratory interactions in this section.
2. Provide mechanisms of interaction if available, as well as practical instructions for preventing or managing these interactions. You should perform a literature search in this regard and provide the findings with references in your response.
3. Proposed labeling should include subsections for Renal Impairment and Hepatic Impairment under the Use in Specific Populations Section 8.0. Include all information

relevant to use and dosing in these specific subpopulations. A literature search in this regard is recommended.

4. Organize the Clinical Pharmacology Section 12.0 of the proposed labeling into Mechanism of action (12.1), (b) (4) and Pharmacokinetics (12.3).
5. Provide method suitability studies for the sterility test.
6. Provide method suitability studies for the endotoxin test.
7. Submit Patent Information with authorized signature on FDA Form 3542a, per 21 CFR 314.53(c)
8. We note that you have not submitted a request for proprietary name review. If you intend to have a proprietary name for this product, we request that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

During our preliminary review of your submitted labeling, we identified the following labeling format issues:

Highlights (HL):

1. Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. See DOSAGE and ADMINISTRATION, 2.1.
2. The **Highlights Limitation Statement** must be placed at the beginning of HL, **bolded**, and reads as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
3. The **Product Title** must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
4. The **Patient Counseling Information Section** must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”
5. White spacing between headings must be consistent

Contents: Table of Contents (TOC)

1. Align Right column with left column
2. Begin right column with a heading, not a subheading

Full Prescribing Information (FPI):

1. The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
2. Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
3. Patient Counseling Information, Section 17 :
 - a. This section is required and cannot be omitted.
 - b. Must reference any FDA-approved patient labeling, including the type of patient labeling.

We request that you resubmit labeling that addresses these issues by April 26, 2011. The resubmitted labeling will be used for further labeling discussions.

We recognize that further characterization of the nonclinical safety of sodium glycerophosphate is not required, however, Sodium Glycerophosphate is considered a new active ingredient. 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 (b) (4) for this application. Once we have reviewed your request, we will notify you if the (b) (4) request is denied and (b) (4)

If you have any questions, call Frances Fahnbulleh, Regulatory Project Manager, at (301) 796-0942.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
04/12/2011



NDA 200,656

NDA ACKNOWLEDGMENT

APP Pharmaceuticals, LLC
A Company of the Fresenius Kabi Group
Attention: Aparna Dagar, PhD.
Senior Regulatory Scientist
1501 East Woodfield Rd., Suite 300E
Schaumburg, IL 60173

Dear Dr. Dagar:

We have received your New Drug Application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Kabiven and (b) (4)

Date of Application: January 28, 2011

Date of Receipt: January 28, 201

Our Reference Number: NDA 200,656

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 March 29, 2011 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.

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 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>.

If you have any questions, call me at (301) 796-0942.

Sincerely,

{See appended electronic signature page}

Frances Fahnbulleh, PharmD.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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/s/

FRANCES G FAHNBULLEH

03/01/2011

NDA Ack letter

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 20, 2011

TIME: 1:00pm EST

APPLICATION: NDA 200656

DRUG NAME: Kabiven and (b) (4)

TYPE OF MEETING: T-con

MEETING RECORDER: Frances Fahnbulleh, PharmD (RPM)

FDA ATTENDEES:

Division of Gastroenterology and Inborn Errors Products and DMPQ

Francis Godwin, Office Compliance, Division of Manufacturing and Product Quality

Raphael Brykman, Office of Compliance, DMPQ

Tarun Mehta, PhD, CMC Reviewer, ONDQA

Frances Fahnbulleh, PharmD, Project Manager (DGIEP)

Marie Kowblansky, PhD, CMC Reviewer, ONDQA(arrived after introductions)

EXTERNAL CONSTITUENT ATTENDEES:

APP Pharmaceuticals

Aparna Dagar, PhD- Sr. Regulatory Scientist

BACKGROUND:

In this NDA, the sponsor indicates that glycine, an amino acid component in the Kabiven product is manufactured at (b) (4), a site that (b) (4)

The t-con is being held to determine the operating status of (b) (4).

MEETING OBJECTIVES:

To determine if the (b) (4) site is currently operational in view of the (b) (4) (b) (4) (b) (4)).

To determine if there are alternative manufacturing sites for glycine (b) (4)

DISCUSSION POINTS:

The sponsor informed the FDA that:

- the site is operational
- there was no damage to the facility
- (b) (4) is currently being done for all lots
- there is a stock pile supply of glycine made (b) (4)
- sponsor is working on potential alternative sites (backup facility) for manufacturing glycine (b) (4)

AGREEMENT REACHED:

The sponsor agreed to provide the following in the response to our Information Request to be submitted to the NDA next week:

- Status on current capability of the (b) (4) site
- Provide details for present and future Quality Assurance testing at this site
- Provide information on the length of time the testing is expected to continue
- Provide preliminary information on potential alternative sites

The meeting ended at 1:20pm EST

Submitted by:

Frances Fahnbulleh, PharmD
Regulatory Health Project Manager

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/s/

FRANCES G FAHNBULLEH
07/20/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND 105,282

APP PHARMACEUTICALS
Att: Aparna Dagar, Ph.D.
1501 East Woodfield Road
Suite 300E
Schaumburg, IL 60173

Dear Dr. Dagar:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Kabiven and

(b) (4)

We also refer to the Type B meeting between representatives of your firm and the FDA on July 20, 2009. The purpose of the meeting was to obtain specific guidance on the requirements for introduction of the firm's products in the United States.

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

If you have any questions, call me at (301) 796-2104.

Sincerely,

{See appended electronic signature page}

Marlène G. Swider, MHSA
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 20, 2009
TIME: 1:00 – 2:00 P.M.
LOCATION: FDA WO Bldg. 22 Room 1315
APPLICATION: PIND 105, 282
DRUG NAME: Kabiven and (b) (4)
TYPE OF MEETING: Type B

MEETING CHAIR: Nancy Snow, D.O., M.P.A.

MEETING RECORDER: Marlene G. Swider, M.H.S.A.

FDA ATTENDEES: (Title and Office/Division)

Donna Griebel, M.D.	Director, Division of Gastroenterology Products (DGP)
Ann Pariser, M.D.	Deputy Director, DGP (Acting)
Hugo Gallo-Torres, M.D., Ph.D., P.N.S.	Resident Expert
Nancy Snow, D.O., M.P.A.	Acting Team Leader, DGP
Tamara Johnson, M.D., M.S.	Clinical Reviewer, DGP
Karyn Berry, M.D.	Clinical Reviewer, DGP
Sushanta Chakder, Ph.D.	Supervisory Pharmacologist, DGP
Lanyan Fang, Pharm.D.	Clinical Pharmacology Reviewer
Marlene Swider, M.H.S.A.	Project Manager, DGP

EXTERNAL CONSTITUENT ATTENDEES:

APP Pharmaceuticals (APP) and Fresenius Kabi (FK):

Lisa McChesney-Harris, Ph.D.	Vice President, Regulatory Affairs (APP)
Aparna Dagar, Ph.D.	Senior Regulatory Scientist (APP)

(b) (4)	
Karin Heimdahl	Vice President, Corporate Regulatory Affairs (FK)
Kirsten Nyland	Executive Vice President, Business Unit Parenteral Nutrition (APP)

BACKGROUND:

1 BACKGROUND

APP requested this Type B meeting to discuss the requirements pertaining to the submission of an NDA for Kabiven and (b) (4). The aim is to revisit and clarify the data and

documentation requirements to support the submission and approval of a singular 505(b)(2) application for the two proposed drug products.

SPONSOR'S QUESTIONS AND FDA PRELIMINARY RESPONSES

Q1: We wish to gain the Agency's agreement that, based on the lack of right of reference to Novamine, Aminosyn, and Glucose clinical data and the current marketing status of the three separate drug products in the US, adequate safety and efficacy information exists to warrant filing a single 505(b)(2) application for the qualitatively identical Kabiven and (b) (4) products for the proposed indication.

FDA Response:

We do not agree. As the total composition of (b) (4) differs from both Novamine and Aminosyn, you must perform clinical trials to prove that (b) (4) (b) (4) is adequately safe and efficacious. Specifically, we are concerned about the electrolyte content of the (b) (4) compared to the proposed reference products. In Aminosyn, there are differences in the amount of both electrolytes and amino acids. In Novamine, there are differences in electrolytes.

You should submit an IND with full information on (b) (4) chemistry, manufacturing and controls (CMC), nonclinical and clinical Phase 1 and 2 trials, as well as similar information for Kabiven and (b) (4) products. For Phase 3 trials, consider trials that compare (b) (4) to Novamine 11.4% with electrolytes added to evaluate number of days on parenteral nutrition for a post-surgical or ICU population. Clinical endpoints to compare new parenteral nutrition formulations with currently approved products should include clinical outcome measures. You may use any number of clinical outcome measures, however, do consider infection rate, mortality, and length of hospital stay. The agency strongly recommends that more than one Phase 3 trial be conducted for each NDA submitted.

Also, please provide the CMC information on the glucose content in the reference product being used. Please confirm that Intralipid 20% is your product.

You will need to show that the mechanism of mixing the three products assures the continuous flow of the mixture and that there are no precipitations issues after mixing.

Discussion:

The sponsor provided a revised table of the component concentrations of Kabiven and (b) (4) after admixture, to supersede Table 2 from the background package. The revised table was to provide a more accurate picture of the concentrations of amino acids and electrolytes in the final product. The sponsor

referred to a 505(b)(2) approval of Clinimix®, which used (b)(4)® as the reference listed product. The sponsor inquired as to how their products differ from Clinimix such that a 505(b)(2) application would not be possible.

Discussion at the meeting centered around electrolytes, and how the amounts in Kabiven and (b)(4) compare to other products on the market. Sponsor stated that the electrolyte concentrations in their products are comparable to those of other approved products, and that only minimal amounts of electrolytes are being added.

FDA expressed concern about the “wide” spectrum of electrolyte quantities present in the product, and sought the scientific basis upon which these quantities are based. The sponsor offered to provide background information to support the minimal amounts of electrolytes used in their products, based largely on guidances provided by experts in the parenteral nutrition field (e.g. ASPEN and ESPEN).

Agency agreed to reconsider the proposal of submitting a 505(b)(2) when additional information from the sponsor on electrolytes is provided.

Q2: With respect to the clinical and nonclinical information provided for sodium glycerophosphate, and the available clinical studies on the overall product, we wish to gain the Agency’s agreement that adequate safety and efficacy has been demonstrated and no additional characterization is required to demonstrate safety and/or efficacy of sodium glycerophosphate for use in humans?

FDA Response:

We agree that further characterization of the nonclinical safety of sodium glycerophosphate is not required.

As stated in the referenced study #8 (Peguero Monforte, 1996), the equivalence (measured as AUC of the plasma or urine levels of phosphate) was not established between sodium glycerophosphate and inorganic phosphate. Thus, we are requesting the sponsor to conduct a cross-over study or studies to demonstrate relative bioavailability using their proposed products and referenced products in both healthy volunteers and indicated patient population.

In addition, since both mixing procedure and sodium glycerophosphate might change the globular size of lipid emulsions, the elimination rate of lipid emulsions might change as a result. Sponsor needs to address this issue.

Discussion:

Sponsor acknowledged FDA recommendations and look forward to provide material requested.

Q3: Would the Agency concur that our proposed CTD structure for the inclusion of the available safety and efficacy information is adequate?

FDA Response:

The proposed CTD structure for the inclusion of the available safety and efficacy information is not adequate. In addition to the overall summaries of clinical and nonclinical studies data for the three component products of Kabiven and (b) (4), (b) (4), it is important to include integrated summaries of efficacy and safety that relate to the use of the 3 chamber bag device.

Discussion:

This response will be revisited once request for more information on Question 1 is addressed by sponsor.

DECISIONS (AGREEMENTS) REACHED:

See below under action items

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

Agency agreed to reconsider the proposal of submitting a 505(b)(2) when additional information from the sponsor on electrolytes is provided.

ATTACHMENTS/HANDOUTS:

Electrolytes Matrix Table provided at the meeting by APP Pharmaceuticals

Component Concentrations after Admixture

Product	Kabiven	(b) (4)	Aminosyn II w/ Electrolytes in Dextrose with Calcium	Clinimix E Sulfite free w/Electrolytes in Dextrose w/Ca	ProcalAmine	Dextrose & Electrolyte 48	TPN Electrolyte	Novamine 11.4%
NDA No (approval)			19-683 (11/07/88)	20-678 (03/26/97)	18-582 (05/06/1982)	17-484 (02/02/79)	18-895 (07/20/84)	17-957 (01/03/78)
Packaging: No of Chambers in Bag	3	3	2	2	1	1	1	
Glucose (mg/mL)	(b) (4)	(b) (4)	250	350	--	50		
Individual Amino Acids (mg/mL)								
Alanine	4.67	3.33	(b) (4)					
Arginine	3.30	2.35						
Aspartic Acid	0.99	0.71						
Cysteine	--	--						
Glutamic Acid	1.64	1.16						
Glycine	2.31	1.64						
Histidine	1.99	1.41						
Isoleucine	1.64	1.16						
Leucine	2.31	1.64						
Lysine	2.63	1.87						
Methionine	1.64	1.16						
Phenylalanine	2.31	1.64						
Proline	1.99	1.41						
Serine	1.31	0.94						
Threonine	1.64	1.16						
Tryptophan	0.55	0.40						
Tyrosine	0.067	(b) (4)						
Valine	2.13	1.52						

Kabiven and (b) (4)
 PIND 105, 282

Type B Meeting
 July 20, 2009

Product	Kabiven	(b) (4)	Aminosyn II w/ Electrolytes in Dextrose with Calcium	Clinimix E Sulfite free w/Electrolytes in Dextrose w/Ca	ProcalAmine	Dextrose & Electrolyte 48	TPN Electrolyte	Novamine 11.4%
Electrolytes (mmol/L)								
Sodium	(b) (4)	(b) (4)	(b) (4)					
Potassium	(b) (4)	(b) (4)						
Magnesium	3.9	2.8						
Calcium	1.9	1.4						
(b) (4) phosphorous	9.7	7.5						
Chloride	(b) (4)	(b) (4)						
Acetate	(b) (4)	(b) (4)						
Sulfate	3.9	2.8						
(b) (4)		(b) (4)						



PIND 105,282

ADVICE/INFORMATION REQUEST

APP Pharmaceuticals, LLC
Attention: Aparna Dagar, Ph.D.
Senior Regulatory Scientist
1501 East Woodfield Road
Suite 300 East
Schaumburg, IL 60173

Dear Dr. Dagar:

Please refer to your Pre-Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Kabiven and (b) (4)

We also refer to your amendment dated August 24, 2009, containing comments in reply to the preliminary responses and discussion at the July 20, 2009 Pre-NDA Type B meeting.

We have the following comments and recommendations addressing your 3 original questions:

Question No.1. We wish to gain the Agency's agreement that, based on the lack of right of reference to Novamine, Aminosyn, and Glucose clinical data and the current marketing status of the three separate drug products in the US, adequate safety and efficacy information exists to warrant filing a single 505(b) (2) application for the qualitatively identical Kabiven and (b) (4) products for the proposed indication.

We agree with the submission of a single 505(b)(2) NDA application for your products, Kabiven and (b) (4). The additional data should be included in the NDA submission as part of your justification for the electrolyte concentrations of Kabiven and (b) (4). Whether this data is adequate to support marketing approval will be an NDA review issue.

Question No. 2. With respect to the clinical and nonclinical information provided for sodium glycerophosphate and the available clinical studies on the overall product we wish to gain the Agency's agreement that adequate safety and efficacy has been demonstrated and no additional characterization is required to demonstrate safety and/or efficacy of sodium glycerophosphate for use in humans?

FDA requires additional characterization of sodium glycerophosphate for use in humans. Although you are proposing a 505(b)(2) submission, the proposed product is different from the referenced product in terms of phosphate. Therefore, you must demonstrate the relative bioavailability between the proposed products and the referenced product by conducting a relative bioavailability study. You may demonstrate the equivalence in healthy subjects only, rather than both healthy subjects and the indicated patient population.

Question No. 3 Would the Agency concur that our proposed CTD structure for the inclusion of the available safety and efficacy information is adequate?

The proposed CTD structure is not adequate. The submission must include available efficacy and safety summaries of clinical trial and nonclinical study data from the literature as they relate to the three component products of Kabiven and [REDACTED] (b) (4), as well as the combined products. It is also important to include an integrated summary of safety that details safety data from the bioavailability study that will be conducted. See "Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, contact Frances Fahnbulleh, Pharm.D. Regulatory Project Manager, at (301) 796-0942.

Sincerely,

{See appended electronic signature page}

Donna J. Griebel, M.D.
Director,
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-105282

GI-1

APP
PHARMACEUTICA
LS

Kabiven and (b) (4)

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/s/

DONNA J GRIEBEL
01/25/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND 105,282

APP PHARMACEUTICALS
Att: Aparna Dagar, Ph.D.
1501 East Woodfield Road
Suite 300E
Schaumburg, IL 60173

Dear Dr. Dagar:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Kabiven and

(b) (4).

We also refer to the Type B meeting between representatives of your firm and the FDA on July 20, 2009. The purpose of the meeting was to obtain specific guidance on the requirements for introduction of the firm's products in the United States.

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

If you have any questions, call me at (301) 796-2104.

Sincerely,

{See appended electronic signature page}

Marlène G. Swider, MHSA
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 20, 2009
TIME: 1:00 – 2:00 P.M.
LOCATION: FDA WO Bldg. 22 Room 1315
APPLICATION: PIND 105, 282
DRUG NAME: Kabiven and [REDACTED] (b) (4)
TYPE OF MEETING: Type B

MEETING CHAIR: Nancy Snow, D.O., M.P.A.

MEETING RECORDER: Marlene G. Swider, M.H.S.A.

FDA ATTENDEES: (Title and Office/Division)

Donna Griebel, M.D.	Director, Division of Gastroenterology Products (DGP)
Ann Pariser, M.D.	Deputy Director, DGP (Acting)
Hugo Gallo-Torres, M.D., Ph.D., P.N.S.	Resident Expert
Nancy Snow, D.O., M.P.A.	Acting Team Leader, DGP
Tamara Johnson, M.D., M.S.	Clinical Reviewer, DGP
Karyn Berry, M.D.	Clinical Reviewer, DGP
Sushanta Chakder, Ph.D.	Supervisory Pharmacologist, DGP
Lanyan Fang, Pharm.D.	Clinical Pharmacology Reviewer
Marlene Swider, M.H.S.A.	Project Manager, DGP

EXTERNAL CONSTITUENT ATTENDEES:

APP Pharmaceuticals (APP) and Fresenius Kabi (FK):

Lisa McChesney-Harris, Ph.D.	Vice President, Regulatory Affairs (APP)
Aparna Dagar, Ph.D.	Senior Regulatory Scientist (APP)

[REDACTED] (b) (4)

Karin Heimdahl	Vice President, Corporate Regulatory Affairs (FK)
Kirsten Nyland	Executive Vice President, Business Unit Parenteral Nutrition (APP)

BACKGROUND:

1 BACKGROUND

APP requested this Type B meeting to discuss the requirements pertaining to the submission of an NDA for Kabiven and [REDACTED] (b) (4). The aim is to revisit and clarify the data and

documentation requirements to support the submission and approval of a singular 505(b)(2) application for the two proposed drug products.

SPONSOR'S QUESTIONS AND FDA PRELIMINARY RESPONSES

Q1: We wish to gain the Agency's agreement that, based on the lack of right of reference to Novamine, Aminosyn, and Glucose clinical data and the current marketing status of the three separate drug products in the US, adequate safety and efficacy information exists to warrant filing a single 505(b)(2) application for the qualitatively identical Kabiven and (b) (4) products for the proposed indication.

FDA Response:

We do not agree. As the total composition of (b) (4) differs from both Novamine and Aminosyn, you must perform clinical trials to prove that (b) (4) is adequately safe and efficacious. Specifically, we are concerned about the electrolyte content of the (b) (4) compared to the proposed reference products. In Aminosyn, there are differences in the amount of both electrolytes and amino acids. In Novamine, there are differences in electrolytes.

You should submit an IND with full information on (b) (4) chemistry, manufacturing and controls (CMC), nonclinical and clinical Phase 1 and 2 trials, as well as similar information for Kabiven and (b) (4) products. For Phase 3 trials, consider trials that compare (b) (4) to Novamine 11.4% with electrolytes added to evaluate number of days on parenteral nutrition for a post-surgical or ICU population. Clinical endpoints to compare new parenteral nutrition formulations with currently approved products should include clinical outcome measures. You may use any number of clinical outcome measures, however, do consider infection rate, mortality, and length of hospital stay. The agency strongly recommends that more than one Phase 3 trial be conducted for each NDA submitted.

Also, please provide the CMC information on the glucose content in the reference product being used. Please confirm that Intralipid 20% is your product.

You will need to show that the mechanism of mixing the three products assures the continuous flow of the mixture and that there are no precipitations issues after mixing.

Discussion:

The sponsor provided a revised table of the component concentrations of Kabiven and (b) (4) after admixture, to supersede Table 2 from the background package. The revised table was to provide a more accurate picture of the concentrations of amino acids and electrolytes in the final product. The sponsor

referred to a 505(b)(2) approval of Clinimix®^{(b) (4)}, which used [REDACTED]® as the reference listed product. The sponsor inquired as to how their products differ from Clinimix such that a 505(b)(2) application would not be possible.

Discussion at the meeting centered around electrolytes, and how the amounts in Kabiven and [REDACTED]^{(b) (4)} compare to other products on the market. Sponsor stated that the electrolyte concentrations in their products are comparable to those of other approved products, and that only minimal amounts of electrolytes are being added.

FDA expressed concern about the “wide” spectrum of electrolyte quantities present in the product, and sought the scientific basis upon which these quantities are based. The sponsor offered to provide background information to support the minimal amounts of electrolytes used in their products, based largely on guidances provided by experts in the parenteral nutrition field (e.g. ASPEN and ESPEN).

Agency agreed to reconsider the proposal of submitting a 505(b)(2) when additional information from the sponsor on electrolytes is provided.

Q2: With respect to the clinical and nonclinical information provided for sodium glycerophosphate, and the available clinical studies on the overall product, we wish to gain the Agency’s agreement that adequate safety and efficacy has been demonstrated and no additional characterization is required to demonstrate safety and/or efficacy of sodium glycerophosphate for use in humans?

FDA Response:

We agree that further characterization of the nonclinical safety of sodium glycerophosphate is not required.

As stated in the referenced study #8 (Peguero Monforte, 1996), the equivalence (measured as AUC of the plasma or urine levels of phosphate) was not established between sodium glycerophosphate and inorganic phosphate. Thus, we are requesting the sponsor to conduct a cross-over study or studies to demonstrate relative bioavailability using their proposed products and referenced products in both healthy volunteers and indicated patient population.

In addition, since both mixing procedure and sodium glycerophosphate might change the globular size of lipid emulsions, the elimination rate of lipid emulsions might change as a result. Sponsor needs to address this issue.

Discussion:

Sponsor acknowledged FDA recommendations and look forward to provide material requested.

Q3: Would the Agency concur that our proposed CTD structure for the inclusion of the available safety and efficacy information is adequate?

FDA Response:

The proposed CTD structure for the inclusion of the available safety and efficacy information is not adequate. In addition to the overall summaries of clinical and nonclinical studies data for the three component products of Kabiven and (b) (4), it is important to include integrated summaries of efficacy and safety that relate to the use of the 3 chamber bag device.

Discussion:

This response will be revisited once request for more information on Question 1 is addressed by sponsor.

DECISIONS (AGREEMENTS) REACHED:

See below under action items

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

Agency agreed to reconsider the proposal of submitting a 505(b)(2) when additional information from the sponsor on electrolytes is provided.

ATTACHMENTS/HANDOUTS:

Electrolytes Matrix Table provided at the meeting by APP Pharmaceuticals

Component Concentrations after Admixture

Product	Kabiven	(b) (4)	Aminosyn II w/ Electrolytes in Dextrose with Calcium	Clinimix E Sulfite free w/Electrolytes in Dextrose w/Ca	ProcalAmine	Dextrose & Electrolyte 48	TPN Electrolyte	Novamine 11.4%
NDA No (approval)			19-683 (11/07/88)	20-678 (03/26/97)	18-582 (05/06/1982)	17-484 (02/02/79)	18-895 (07/20/84)	17-957 (01/03/78)
Packaging: No of Chambers in Bag	3	3	2	2	1	1	1	
Glucose (mg/mL)	(b) (4)	(b) (4)	(b) (4)					
Individual Amino Acids (mg/mL)								
Alanine	4.67	3.33						
Arginine	3.30	2.35						
Aspartic Acid	0.99	0.71						
Cysteine	--	--						
Glutamic Acid	1.64	1.16						
Glycine	2.31	1.64						
Histidine	1.99	1.41						
Isoleucine	1.64	1.16						
Leucine	2.31	1.64						
Lysine	2.63	1.87						
Methionine	1.64	1.16						
Phenylalanine	2.31	1.64						
Proline	1.99	1.41						
Serine	1.31	0.94						
Threonine	1.64	1.16						
Tryptophan	0.55	0.40						
Tyrosine	0.067	(b) (4)						
Valine	2.13	1.52						

Product	Kabiven	(b) (4)	Aminosyn II w/ Electrolytes in Dextrose with Calcium	Clinimix E Sulfite free w/Electrolytes in Dextrose w/Ca	ProcalAmine	Dextrose & Electrolyte 48	TPN Electrolyte	Novamine 11.4%
Electrolytes (mmol/L)								
Sodium	(b) (4)	(b) (4)	(b) (4)					
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Acetate	(b) (4)	(b) (4)						
Sulfate	3.9	2.8						
(b) (4)		(b) (4)						

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- IND 105282	----- GI 1	----- APP PHARMACEUTICA LS	----- Kabiven and (b) (4)

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/s/

MARLENE G SWIDER
08/20/2009