CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200656Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, M.D., M.P.H.
Subject	Division Deputy Director Summary Review
NDA	200656
Applicant Name	APP Pharmaceuticals, LLC (a Fersenius Kabi company)
Date of Submission	11/25/2013 (Resubmission following CR response)
PDUFA Goal Date	August 25, 2014 (original date May 25, 2014; extended 3 months major amendment)
Proprietary Name / Established (USAN) Name	KABIVEN® (amino acids, electrolytes, dextrose and lipid injectable emulsion) PERIKABIVEN® (amino acids, electrolytes, dextrose and lipid injectable emulsion) for intravenous use
Dosage Forms / Strength	A sterile, hypertonic emulsion in a three chamber container. The individual chambers contain one of the following respectively: amino acids and electrolytes, dextrose, or lipid injectable emulsion: KABIVEN: 2,566 mL, 2,053mL, 1,540mL, and 1,026 mL. PERIKABIVEN: 2,400 mL, 1,920 mL, and 1,440 mL.
Proposed Indication(s)	KABIVEN/(PERIKABIVEN) is indicated as a source of calories, protein, electrolytes and essential fatty acids for adult patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. KABIVEN® may be used to prevent essential fatty acid deficiency or treat negative nitrogen balance in adult patients.
Action/Recommended Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review (original and CR response reviews)	Karyn Berry
Pharmacology Toxicology Review	Babatunde Akinshola, Sushanta Chakder
CMC Review	Tarun Mehta
Microbiology Review	Denise Miller
Clinical Pharmacology Review	Sandhya Apparaju
CDTL Review	Ruyi He
OSE/DMEPA	Denise Baugh
PMHS	Donna Snyder, Carrie Ceresa
CDRH HF	Quynh Nguyen
CDRH GHDB	Alan Stevens
Office of Compliance, CDRH	Shanika Booth
OND Office Director Memo (cycle 1)	Julie Beitz

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader
CMC= Chemistry and Manufacturing
CDRH= Center for Devices and Radiologic health
HF = Human Factors
GHDB=General Hospital Devices Branch

1. Introduction

Kabiven and Perikabiven (amino acids, electrolytes, dextrose and lipid injectable emulsion) are total parenteral nutrition systems. The products are a source of calories, protein, electrolytes and essential fatty acids for adult patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Kabiven and Perikabiven are designed to provide sterile solutions using innovative 3- chamber bag technology. Kabiven is administered by central vein only, whereas Perikabiven may be administered by either central or peripheral vein. The doses delivered would be individualized and would depend on the patient's clinical condition, body weight and nutritional requirements. Kabiven and Perikabiven are packaged in several sizes (Kabiven: 1026mL, 1540mL, 2053mL, 2566mL, and Perikabiven: 1440mL, 1920mL and 2400L).

The Applicant proposed tha (b) (4)

2. Background

This submission, November 25, 2013, is a complete class 2 re-submission to the FDA Complete Response letter. The original application was submitted to the FDA on January 28, 2011. It was filed as a 505(b)(2) application and referenced the Agency's finding of safety and effectiveness for the following products:

1. Intralipid 20% Injection, NDA 018449 (Fresenius Kabi Deutschland Gmbh)
2. Intralipid 20% Injection, NDA 020248 (Fresenius Kabi Deutschland Gmbh)
2. Novamine 11.4% Injection, NDA 017957 (Hospira, Inc.)
3. Aminosyn II 3.5%, with electrolytes in dextrose injection with calcium, NDA 019683 (Hospira, Inc.)
4. Clinimix E 2.75/10 Injection, sulfite-free with electrolytes, NDA 020678 (Baxter Healthcare Corp.)

On November 20, 2011 the FDA sent the Applicant a Complete Response letter which contained several deficiencies. These deficiencies will be addressed in this review. The items are listed in the Office Director Review (Appendix 1), and the reader is directed to that review for a more information regarding the first cycle findings.

During the original NDA review cycle these products were considered to be NMEs. However, as noted by the Office Director memo, the matter of whether or not these products are NMEs must be further clarified. In the first review cycle the following information was considered and a preliminary conclusion that this was an NME was made:

> "The intravenous fat emulsion component of Kabiven and Perikabiven is identical to that of approved Intralipid 20%. The amino acid component, (b) (4) (b) (4) to, approved Novamine 11.4% (e.g., (b) (4)

[redacted], whereas Novamine contains [redacted]. The dextrose component differs between the two products, as Kabiven and Perikabiven contain [redacted] and [redacted] dextrose, respectively. The electrolyte components of Kabiven and Perikabiven do not exactly correspond to that of Aminosyn II 3.5% or Clinimix E; in particular, Kabiven and Perikabiven contain sodium glycerophosphate, an organic form of phosphate. Sodium glycerophosphate is hydrolyzed in vivo by nonspecific phosphatases to release phosphate. The Applicant contends that this organic form of phosphate [redacted] a potentially life-threatening complication that can be associated with inorganic phosphate. Although sodium glycerophosphate is commercially available under monograph, this is the first use as an active ingredient in a drug product, and is, therefore, considered a new molecular entity".

However, during the current review, further consideration of these facts resulted in the conclusion that this was NOT an NME, rather a new active ingredient.

On May 13, 2014, the CMC precedence committee met and decided that there are no NMEs used in this application. The committee determined that sodium glycerophosphate is used as an active ingredient to supply phosphate and is therefore considered a new active ingredient. Therefore, the final approval will be signed at the Division level.

3. CMC/Device

CMC

The CMC review dated May 21, 2014 addressed the outstanding issues related to CMC deficiencies. Below find summaries of the findings. In addition it was noted that the EES was acceptable, and the EA was granted a categorical exclusion.

Deficiency:

Information submitted did not delineate the levels of selected heavy metals that may be present in each chamber of the 3-chamber bag. The Applicant will need to submit this information and develop specifications and acceptance criteria to control the levels of these heavy metals in each chamber.

According to the CMC review this deficiency has been satisfactorily resolved.

"The Applicant revised the specification of the drug product in line with recommendation of ICH Q3D with validation of analytical method L73 (ICP-SFMS), for the determination of arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), mercury (Hg), manganese (Mn), lead (Pb), selenium (Se) and zinc (Zn) in mixed fat emulsion product by ICP-SFMS".

"Analytical data showed the amount of each specified heavy metal is well below the acceptance criterion. Also submitted information is the total volume of emulsion after three chambers are opened and mixed, which will help to determine the total amount of heavy metals to be exposed to the patients".

Deficiency:
Expiration dating requires more data to be reviewed during the second cycle.

According to the CMC review this deficiency has been satisfactorily resolved.

"The particulate matter problem caused by (b) (4) from the stopper on the bag has been rectified. Specification for the stopper has been established with a limit of < (b) (4) ppm. A new batch for Kabiven and Perikabiven was manufactured with the new stopper, and particulate matters were monitored for up to 18 months at a long term condition. Data showed no more particulate matters were found."

In addition "On May 27, 2014, additional stability data up to 24 months was submitted in the amendment 0033 with satisfactory results including no particulates observed in the product bags." (noted in CMC review 6/10/14)

"Therefore, the expiration dating period for both products can be extended to 24 months".

Deficiency:
The Applicant must confirm that the primary container/closure system (i.e., (b) (4)) meets (b) (4)

According to the CMC review this deficiency has been satisfactorily resolved.

" (b) (4) which are used in the inner layer of the bag are (b) (4) safe food contact materials."

"The leachable study was performed on (b) (4) and the data submitted in (b) (4) for the NDA 17,643 for Intralipid. After further research on (b) (4) exposure, the non-clinical pharmacology reviewer has determined that this is not a safety concern."

Deficiency:
Satisfactory resolution of deficiencies identified during the inspection of the (b) (4) . manufacturing facilities in (b) (4) and the Fresenius Kabi manufacturing facility in Sweden is required before the application may be approved.

According to the CMC review this deficiency has been satisfactorily resolved.

"The Office of Compliance has issued an "Acceptable" recommendation for this application".

Deficiency:
The Applicant will be notified that deficiencies involving DMF # (b) (4) were conveyed by the Agency on (b) (4) to the DMF holder, (b) (4). These deficiencies will need to be addressed before the application may be approved (these deficiencies involve controls for impurities in the (b) (4) drug substance).

According to the CMC review this deficiency has been satisfactorily resolved:

"The deficiency noted for the DMF # (b) (4) (for the drug substance, (b) (4)), was corrected and it is now deemed adequate to support this NDA".

On June 10, 2014 the CMC review indicated that "based on the revised labels for the immediate container/closures as well as conformance of the storage temperature in the "How Supplied" section of PI to the USP format, this NDA is now recommended for APPROVAL from the ONDQA perspective with an expiration dating period of 24 months.

Clinical Microbiology Review:
No new data was submitted. The original application was reviewed and recommended for approval on 9/21/2011.

DEVICES:
Deficiencies:
The Applicant will need to address deficiencies regarding device performance. Use-related hazards will need to be identified and mitigated; appropriate human factors studies will be needed to address any specific hazards that are identified.

CDRH Human Factors (HF) review of two validation study reports was performed during this review cycle. The results and conclusions from the CDRH HF review are provided below.

Study 1:
"Fifteen healthcare professionals (8 pharmacists and 7 pharmacy technicians) participated in the human factors validation of the training provided by the Sponsor for use of the Kabiven and Perikabiven 3 chamber parenteral nutrition (PN) bags. This is a supplemental study, to determine the efficacy of the training in mitigating all use errors observed with pharmacists and pharmacy technicians."
"This summative study evaluated the following user tasks for the 3 chamber bags:

- Choosing the correct bag per the PN order
- Inspecting the bag
- Removing the overpouch
- Activating the bag
- Injecting additives"

"The training session included a 5 minute instructional video, live demonstration, and hands-on skills lab. There was a 24 hour lag time between the training and task evaluation. Each participant executed 3 PN orders by completing the above tasks and then answered labeling validation and post-test questions. No use errors or close calls were observed during this testing."

Study 2:
"Fifteen home care nurses participated in the human factors validation study for Kabiven and Perikabiven 3 chamber parenteral nutrition (PN) bags for use in the home care setting. This summative study evaluated the adequacy of the instructional materials provided by Fresenius to provide home care nurses with the ability to self-train and then impart the knowledge to train a simulated patient on the proper use of Kabiven and Perikabiven 3 chamber PN bags". "These tasks included:

- Inspecting the bag
- Activating the bag
- Injecting additives
- Spiking the bag"

"All participants except one participant that did not activate the bag completely but this participant realized her error when she saw the fluid escaping from the lipid chamber. She subsequently checked the homogeneity of the bag content, and believed that the contents were evenly distributed".

The CDRH HF reviewer concluded that the studies were acceptable. The reviewer made the point that the training helped to mitigate errors associated with the 3-chamber parenteral nutritional bag. They requested that the in-service training guide will be used in the sponsors training program.

Additional comments regarding these studies from the Division of Medication Error Prevention and Analysis (DMEPA [OSE]) are as follows:

"The Applicant noted that no further revisions to the container label or prescribing information are necessary in light of the results from the 2 studies. We agree with the Applicant and note that the IFU provides detailed diagrams appropriately located (e.g., adjacent to the narrative), use of bold and large font sizes to increase the prominence of important statements on the bag label, and appropriate use of redundancy (e.g., identical information in the section titled "Read This" on the over pouch labeling and the bag label). We find the proposed container label and prescribing information acceptable."

DMEPA concluded that "DMEPA finds the study design and results for the (supplemental) validation study involving pharmacy personnel and the usability study involving home care nurses acceptable. These studies have also addressed previous failures cited by DMEPA. Additionally, we conclude that the proposed container label and instructions for use are adequate."

I have reviewed this issue and have found that the training video will be posted on the Applicant's website. In addition, access information to this site is also reflected in label section *2.2 Important Preparation Instructions*: "An instructional video is available at www.KabivenUSA.com".

Based upon these reviews, I find that this deficiency has been satisfactorily resolved.

Device Engineering
The CDRH General Hospital Devices Branch (GHDB) review focused on resolving device engineering deficiencies for leaking, burst, dropping, and infusion port leaking. The CDRH GHDB review concluded that no additional device engineering deficiencies remain.

This deficiency has been satisfactorily resolved.

In summary, I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. The CMC deficiencies listed in the CR letter have been satisfactorily resolved.

I concur with the conclusions reached by the CDRH Human Factors and General Hospital Devices Branch regarding the satisfactory resolution of the deficiencies regarding the 3-chamber bag that are listed in the CR letter.

I concur with the conclusions reached by the CDRH General Hospital Devices Branch regarding the satisfactory resolution of the deficiencies regarding engineering deficiencies that are listed in the CR letter.

There are no outstanding issues precluding approval.

4. Nonclinical Pharmacology/Toxicology

I have reviewed the nonclinical review and the team leader addendum which further clarifies some of the analysis. The reviewer's summarized the findings as follows:

"In the current submission, the Applicant has submitted a complete safety assessment of leachables/extractables from the 3-CB (b) (4) packaging system. Safety assessment of the potential leachables from the 3-CB packaging system was performed following (b) (4) and storage of the 3-CB (b) (4) bags with components of the drug product (lipid, glucose and amino acid), or treatments with comparable solvents, such as saline, water or 13 % ethanol stored in the (b) (4) container for extended period at different temperatures after (b) (4) to allow leaching of the migrants from the container into the liquids. The levels of leachables and extractables and their degradation products were measured, analyzed, and an assessment of the safety was performed. For some components, for which the levels were not detectable because of insolubility or for some other reason, the safety assessment of that component was performed based on the assumption that 100% of it will be released into the IV fluid".

"The calculated maximum potential exposure to the leachables/migrants under the worst case scenario was lower than or at least, equal to the PDE (permitted daily exposure) calculated from the available nonclinical data for each component of the (b) (4) 3-CB packaging system. There is a clear separation between the estimated maximum patient exposure to the migrants (or their degradation products) and the exposures considered to be safe based on animal data. Thus, there are no safety concerns for the potential leachables/extractables from the (b) (4) 3-CB packaging system into Kabiven/Perikabiven IV fluids".

Because this is a new container, it was important to understand the profile of the leachables/extractables. In the review of (b) (4) in particular, the safety margin was acceptable and sufficient from a nonclinical, chemistry and manufacturing, clinical standpoint for approval of this product. However, it was agreed that additional measurements should be performed post-marketing in order to ensure that the variability of the concentration of (b) (4) is small, and that it continues to be within acceptable limits. This was agreed upon as a post-market commitment by the Applicant.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

There were no outstanding issues relating to clinical pharmacology. The reviewers concluded that the NDA was approvable during the first cycle. Comments for the final labeling regarding Clinical Pharmacology were addressed by the sponsor. See final approved labeling.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval for use in adult patients.

6. Clinical Microbiology

Does not apply to this application.

7. Clinical/Statistical-Efficacy

The clinical reviewer provided a summary of the clinical pharmacology study which was evaluated in the first review cycle (see below).

"During the first review cycle, efficacy of this application was assessed by a clinical pharmacology study. The Applicant submitted a relative bioavailability study (Study Glyc-001-CP1) to provide pharmacokinetic bridging of the phosphate moiety in order to justify the change from inorganic phosphate to sodium glycerophosphate (novel organic phosphate source) that is proposed for use in both Kabiven and Perikabiven".

"The results of Study Glyc-001-CP1 demonstrated comparability of phosphate provision from the new organic sodium glycerophosphate to that of equimolar doses of the approved inorganic phosphate. The relative bioavailability results supported incorporation of sodium glycerophosphate as a source of phosphate provision into the proposed PN products."

There were eleven small, supportive, Kabiven and Perikabiven clinical trials of short-term duration submitted during the first cycle, as noted by the clinical reviewer. None of the clinical trials had clinical efficacy endpoints, but three of the Kabiven trials had laboratory assessments. These studies collected blood/serum samples and performed various laboratory tests. (for complete review see first cycle clinical review). No pre-specified clinical efficacy outcomes were monitored in these studies. The efficacy of the components of

Kabiven/Perikabiven for the indication proposed are supported by our determination of efficacy from other products referenced in this 505 (b)(2) application (mentioned above).

8. Safety

The clinical reviewer summarized the safety issues for this cycle as follows:

"The safety issues related to this application include the need for pediatric safety studies to assess safe and effective dosing of these products in this population and the presence of phytosterols in IVFE component of these products and their safety implications"

"Phytosterols are impurities present in IVFE products and their presence is a potential safety issue. Phytosterols have been implicated as a causative factor of parenteral nutrition associated liver disease (PNALD), especially in pediatric and neonatal patients.
As a potential safety issue, there is a clinical need to assess/characterize the sterols found in these products. (b) (4), (b) (5)

"The Applicant reported that no additional nonclinical or clinical studies/trials have been conducted with Kabiven or Perikabiven since the filing of the NDA. Therefore, no updated safety information related to studies/clinical trials is available for this sub-mission."

"The Applicant did submit Periodic Safety Update Report (PSUR) 009/01 (FEB 2011 to JAN 2013). Based on the current safety data for Kabiven and Perikabiven, the safety profile has not altered. This current PSUR submitted by the Applicant did not identify any new safety hazards".

"Kabiven is registered in 61 countries and Perikabiven is registered in 67 countries. The Applicant reported no changes in foreign labeling. During the period covered by the report, no actions related to safety have been taken by regulatory authorities. The Applicant reported that a review of the literature revealed no new or yet unknown risks in relation to the administration of Kabiven / Perikabiven, which would require a change of the risk-benefit-ratio."

I am in agreement with the safety evaluation of Kabiven and Perikabiven as described above. The safety issues are represented clearly in the agreed upon approved labeling attached to the approval letter.

9. Advisory Committee Meeting

This application was not referred to the Gastrointestinal Drugs Advisory Committee for discussion because the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions on the role of the products in the

diagnosis, cure, mitigation, treatment or prevention of a disease, and outside expertise was not necessary.

10. Pediatrics/Maternal Health

Deficiency:
The applicant has not provided (b) (4) To address this deficiency, the Applicant must submit a pediatric plan that outlines the pediatric studies it will conduct, a timeline for completion of these studies, evidence that studies are being conducted with due diligence, and grounds for study deferral.

The Pediatric and Maternal Health Staff (PMHS) was consulted to assess the acceptability of the applicant's request that (b) (4)

In a letter dated September 8, 2011, the Agency informed the Applicant that (b) (4)

On May 9, 2014, the Applicant submitted the following pediatric study proposal as a post-marketing study:

"The proposed study (b) (4) is now planned to be conducted (b) (4) age groups (2– 16), with the same study design as originally proposed. A representative number of patients (b) (4) will be included to assess safety. No other substantive changes are proposed to the study outlines submitted in October 2011 (SEQ 0014)". In addition the Applicant submitted proposed timelines for completion of this study.

In order to prepare for the PERC committee meeting, PMHS recommended that the Division request that the Applicant provide additional information to (b) (4). Because nutritional needs vary based on the age and weight of the patient, and because Kabiven and Perikabiven are fixed dose combinations, these products may not be appropriate

to meet the nutritional needs of pediatric patients below a certain weight or age. PMHS also agrees that additional safety studies are warranted (b) (4)

On June 18, 2014 the PeRC committee discussed the Applicant's pediatric plans and request for a partial waiver. The PeRC agreed with the Division to grant a partial waiver in patients < 2 years of age because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. Pediatric patients < 2 years of age generally require specific, individually prepared parenteral nutrition. In addition, PeRC recommended that a deferral of trials in patients ≥ 2 years of age be granted because this product is ready for approval for use in adults and the pediatric study have not been completed.

The PeRC also agreed with the Division's plan to require a PREA PMR 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 agreed that studies in Perikabiven would not be needed.

11. Other Relevant Regulatory Issues

Hospira, Inc. submitted a request to withdraw NDA 019683 for Aminosyn II 3.5% Injection on (b) (4), and on (b) (4), a request to withdraw NDA 017957 for Novamine 11.4% Injection. Hospira stated that the products were not currently marketed and (b) (4) This application refers to these listed drugs. Before this application may be approved, the Agency will need to determine whether Aminosyn II 3.5% Injection and Novamine 11.4% Injection were withdrawn for reasons of safety or effectiveness. Since the application will not be approved during this review cycle, the Agency's determination will be deferred to this review cycle.

Review of this issue revealed that Aminosyn II 3.5% Injection and Novamine 11.4% Injection were not removed for safety or efficacy. Therefore, the information from these products can be relied upon for approval of Kaviven and Perikabiven.

Finally, The Applicant, APP Pharmaceuticals, LLC, a wholly owned subsidiary of Fresenius Kabi, submitted a letter from Fresenius Kabi dated November 11, 2011 granting right of reference to NDA 018449. Therefore, APP no longer needs to rely upon the Agency's finding of safety and effectiveness for Intralipid 20% because they can now reference the data in NDA 018449 directly.

- Financial Disclosure: satisfactorily addressed (see clinical review)
- Proprietary name Review:

The Applicant submitted correspondence on November 22, 2013 requesting review of their proposed proprietary names, Kabiven (for the central formulation) and Perikabiven (for the central/peripheral formulation). OMEPM reviewed this request and found the proposed proprietary names of Kabiven and Perikabiven acceptable.

There are no other unresolved relevant regulatory issues.

12. Labeling

Includes:

- Proprietary name

  There were several discussions regarding the actual name that should be used in the labeling. The final determination was: (amino acids, electrolytes, dextrose and lipid injectable emulsion), for intravenous use.

  It was further determined that "(b) (4)" should not be included as part of the name. The CMC review team required the Applicant to submit the data which supported that statement. Based upon the Applicant's response, it was concluded that sulfites were not added but actual measurement of sulfites in the product was not available. Therefore it was recommended that the Applicant replace the phrase "(b) (4)" with "No added sulfites" in the *Description (11)* section of labeling, and that this phrase not appear next to the Trade name. This was accepted by the Applicant.

- Physician labeling

  -Since this application was based on 505(b) (2) references several of which are not in PLR format, sections of the label, particularly the Warnings and Precautions were updated to be in line with current labeling guidances and the CFR.

  -The Dosing and Administration section was updated to a more user friendly format including current references regarding nutritional requirements ([Ayers P. et al. A.S.P.E.N. Parenteral Nutrition Handbook, 2nd ed. 2014 pg. 123]; [Mueller CM ed. The A.S.P.E.N. Nutrition Support Core Curriculum 2nd ed. 2012. Chapter 29 Wolk R, Foulks C. Renal Disease., pg. 500]).

  -The Maternal Health Team was consulted to assist in the wording of the pregnancy subsection of the label. This resulted in recommendations structured in the spirit of the Proposed Pregnancy and Lactation Labeling Rule (PLLR) published May 2008, while complying with current labeling regulations. The nursing mothers subsection of labeling was revised to comply with current labeling recommendations. The Applicant accepted these recommendations.

- Carton and immediate container labels

  The agreed upon carton and container labeling will change proposed wording "(b) (4) (b) (4)" to "no sulfites added". This change was submitted by the Applicant on 8/21/2014). It was acceptable to the CMC review team.

  The Applicant informed the Division that it was unable to have these changes reflected in the printing template for the immediate container label for up to 8 weeks from the agreed upon labeling. Since these formulations of lipid emulsions are in short supply,

we permitted the Applicant to be able to use the current printing template for the carton and container which includes the term "(b) (4)", until which time the new template is available and then it will match the approved wording: "No sulfites added" as noted above by the CMC reviewers.

- Patient Labeling/Medication Guide
  None necessary, this will be parentally administered by health care professionals.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action: Approval**

- **Risk Benefit Assessment**

This 505(b)(2) application relies upon the findings of the efficacy and safety of previously approved products as outlined above. Because this preparation is a fixed dose combination, it is anticipated to be useful for supplying the typical adult patient's nutritional needs pareterally. However, in circumstances such as renal failure, or cardiovascular instability it may not be appropriate to administer these fixed dose combination products without supplementation or correction of underlying pathologies. These safety issues are adequately discussed in the agreed upon labeling. Kabiven and Perikabiven will be used in centers where knowledgeable clinicians, pharmacists and nutritionists are will direct the use of these products. In conclusion, there is a favorable benefit-risk profile when Kabiven or Perikabiven are used for adult patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

A REMS is not recommended for this product

- **Recommendation for other Postmarketing Requirements and Commitments**

PMR:
2772-1 Prospective, randomized (1:1), open-label, parallel group, active controlled, multicenter trial study to assess safe and effective doses of Kabiven (amino acids, electrolytes, dextrose and lipid injectable emulsion) in pediatric patients aged 2 to 16 years.

Final Protocol Submission:	02/2015
Study Completion:	08/2017
Final Report Submission:	08/2018

PMC:
2772-2 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

APPENDIX I (see next page)

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

/s/

JOYCE A KORVICK
08/25/2014

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: November 20, 2011

TO: NDA 200656
Kabiven and Perikabiven (lipid injectable emulsion with amino acids and electrolytes and dextrose)
APP Pharmaceuticals, LLC (a Fresenius Kabi company)

FROM: Julie Beitz, M.D.
Director, Office of Drug Evaluation III

RE: Complete Response Action

Kabiven and Perikabiven (lipid injectable emulsion with amino acids and electrolytes and dextrose) are total parenteral nutrition systems. The products are a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition and would be indicated for the prevention of essential fatty acid deficiency (b) (4) or treat negative nitrogen balance (b) (4) (b) (4)

Kabiven and Perikabiven are designed to provide sterile solutions using innovative 3-chamber bag technology. Kabiven is administered by central vein only, whereas Perikabiven may be administered by either central or peripheral vein. The applicant proposes tha (b) (4)

This memorandum documents my concurrence with a complete response action for the Kabiven and Perikabiven products.

Before this application may be approved, the applicant will need to address several deficiencies. The applicant has not provided sufficient information to (b) (4) To address this deficiency, the

applicant must submit [redacted].

The applicant will need to address deficiencies regarding device performance. Use-related hazards will need to be identified and mitigated; appropriate human factors studies will be needed to address any specific hazards that are identified.

Information submitted did not delineate the levels of selected heavy metals that may be present in each chamber of the 3-chamber bag. The applicant will need to submit this information and develop specifications and acceptance criteria to control the levels of these heavy metals in each chamber.

The applicant must confirm that the primary container/closure system (i.e., [redacted]) [redacted].

Discussions regarding product labeling and postmarketing study requirements or commitments remain unresolved. Satisfactory resolution of deficiencies identified during the inspection of the [redacted] manufacturing facilities in [redacted], and the Fresenius Kabi manufacturing facility in Sweden is required before the application may be approved.

In addition, in the complete response letter, the applicant will be notified that deficiencies involving DMF [redacted] were conveyed by the Agency on August 31, 2011 to the DMF holder, [redacted] These deficiencies will need to be addressed before the application may be approved.[1]

Product Description

Kabiven and Perikabiven are sterile parenteral nutrition products, each comprised of [redacted] drug substances representing seventeen amino acids, [redacted] electrolytes, glucose monohydrate, and purified soybean oil. The products are designed so that the dextrose solution, the amino acid and electrolyte solutions, and the fat emulsion are each contained between the chambers are broken and their contents are admixed. An additive port provides flexibility to include vitamins and other ingredients. Kabiven is manufactured in four packaging sizes delivering a total of 1026, 1540, 2053, or 2566 mL; Perikabiven is manufactured in three sizes: 1440, 1920 and 2400 mL.

There are currently no 3-chamber bag products approved in the US that provide an all-in-one source of total parenteral nutrition. Individually approved 1-chamber or 2-chamber bag products are co-administered to provide the necessary nutritional requirements.

Regulatory Considerations

Kabiven and Perikabiven are manufactured by Fresenius Kabi and have been approved in Sweden since 1999 for adults and pediatric patients 2 years of age and above. Kabiven

[1] These deficiencies involve controls for impurities in the [redacted] drug substance. *See* **Product Quality**.

and Perikabiven have been registered in 58 and 53 countries, respectively.

On January 28, 2011, APP Pharmaceuticals, LLC, a subsidiary of Fresenius Kabi, submitted NDA 200656 for Kabiven and Perikabiven. In accordance with previous Agency advice, the application was submitted as a 505(b)(2), and referenced the Agency's findings of safety and effectiveness for the following products:

1. Intralipid 20% Injection, NDA 018449 (Fresenius Kabi Deutschland Gmbh)
2. Intralipid 20% Injection, NDA 020248 (Fresenius Kabi Deutschland Gmbh)
2. Novamine 11.4% Injection, NDA 017957 (Hospira, Inc.)
3. Aminosyn II 3.5%, with electrolytes in dextrose injection with calcium, NDA 019683 (Hospira, Inc.)
4. Clinimix E 2.75/10 Injection, sulfite-free with electrolytes, NDA 020678 (Baxter Healthcare Corp.)

The intravenous fat emulsion component of Kabiven and Perikabiven is identical to that of approved Intralipid 20%. The amino acid component, [redacted] approved Novamine 11.4% (e.g., [redacted], whereas Novamine contains [redacted]). The dextrose component differs between the two products, as Kabiven and Perikabiven contain [redacted]% and [redacted]% dextrose, respectively. The electrolyte components of Kabiven and Perikabiven do not exactly correspond to that of Aminosyn II 3.5% or Clinimix E; in particular, Kabiven and Perikabiven contain sodium glycerophosphate, an organic form of phosphate. Sodium glycerophosphate is hydrolyzed *in vivo* by nonspecific phosphatases to release phosphate. The applicant contends that this organic form of phosphate [redacted] a potentially life-threatening complication that can be associated with inorganic phosphate. Although sodium glycerophosphate is commercially available under monograph, this is the first use as an active ingredient in a drug product, and is, therefore, considered a new molecular entity.

Sodium glycerophosphate provides for [redacted]% of the phosphate in Kabiven and Perikabiven. The remaining [redacted]% is derived from egg phospholipid, used as [redacted] in the Intralipid component. Because of the relatively large amount of phosphate that is contributed by egg phospholipid, it is considered to be an active ingredient rather than an excipient. As this is the first use of egg phospholipid as an active ingredient in a drug product, it is also considered a new molecular entity.

This application was not referred to the Gastrointestinal Drugs Advisory Committee for discussion because the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions on the role of the products in the diagnosis, cure, mitigation, treatment or prevention of a disease, and outside expertise was not necessary.

Hospira, Inc. [redacted] NDA 019683 for Aminosyn II 3.5% Injection on [redacted], and on [redacted], [redacted] NDA 017957 for Novamine 11.4% Injection. Hospira stated that the products were not currently marketed and [redacted]

[redacted]. This application refers to these listed drugs. Before this application may be approved, the Agency will need to determine whether Aminosyn II 3.5% Injection and Novamine 11.4% Injection were [redacted] Since the application will not be approved during this review cycle, the Agency's determination will be deferred to the next review cycle.

On November 4, 2011, the Agency informed the applicant in writing that deficiencies in the application preclude discussion of product labeling and postmarketing commitments or requirements.

The applicant, APP Pharmaceuticals, LLC, a wholly owned subsidiary of Fresenius Kabi, submitted a letter from Fresenius Kabi dated November 11, 2011 granting right of reference to NDA 018449. Therefore, APP no longer needs to rely upon the Agency's finding of safety and effectiveness for Intralipid 20% because they can now reference the data in NDA 018449 directly.

Clinical Pharmacology

Formal pharmacokinetic bridging for all active components was not deemed necessary. However, to support the inclusion of sodium glycerophosphate, a new molecular entity, in the Kabiven and Perikabiven products, the applicant submitted the results of two relative bioavailability studies. Study Glyc-001-CP1 compared phosphate provision from equimolar doses (a total of 80 mmol infused over 4 hours) of two different phosphate sources (IPhosphate, Hospira, Inc. vs. Glycophos, Fresenius Kabi) in 24 healthy volunteers, ages 18-45 years. The products were infused via peripheral vein. The phosphate content of meals and water was standardized. The pharmacokinetic profile of the two different phosphate sources was found to be similar, though not strictly bioequivalent on all parameters.

Study KABI-003-CP1 explored the relative bioavailability of phosphate provision from organic sodium glycerophosphate administered alone compared to administration as a component of Perikabiven in 10 healthy volunteers, ages 18-45 years. Equimolar amounts of phosphate were provided as either Perikabiven (0.101 mmol phosphate/13.3 mL Perikabiven/kg body weight) or as Glycophos (0.101 mmol Glycophos/13.3 mL NaCl/kg body weight). The products were infused over 8 hours. No significant differences in serum phosphate levels were observed when sodium glycerophosphate was given alone or as a component of Perikabiven. Results from this study however were not considered supportive due to confounding by the contribution of phosphate from food sources that exceeded study drug doses.

Efficacy

Results from ten randomized and one open-label clinical trial conducted in adult patients requiring parenteral nutrition were submitted in support of the efficacy of Kabiven and Perikabiven. These trials were of short duration (7 days) with the exception of one trial which was 4 weeks in duration. None of the Perikabiven trials administered the product via central vein. None of the active comparator products in these trials have been approved for use in the US, and only three trials were designed with pre-defined analyses of efficacy. Nonetheless, laboratory assessments in patients receiving Kabiven products

or comparators produced similar results, including assessments of: serum amino acid and fatty acid patterns, serum levels of pre-albumin, insulin, triglycerides, urea, creatinine, and C-reactive protein, and urinary excretion of amino acids, nitrogen, urea and creatinine.

Safety

Parenteral nutrition products are associated with a number of well-recognized safety concerns. These include the risk of 1) clinical toxicity from heavy metal contamination of product components during their manufacture (e.g., chromium and manganese toxicities), 2) metabolic complications such as hyperglycemia or hypoglycemia, refeeding syndrome, electrolyte imbalances, lipid abnormalities, acid-base disturbance, hepatobiliary disorders and bone disease, and 3) complications related to vascular access, including catheter occlusion and thrombosis, and catheter-related infection and sepsis.

A total of 145 subjects have received Kabiven and 93 have received Perikabiven in clinical trials. The mean age of subjects treated with Kabiven was 59 years, and the mean body mass index (BMI) was 24 kg/m^2. The mean age of subjects treated with Perikabiven was 57 years and the mean BMI was 22 kg/m^2. There were no treatment-related deaths or serious adverse events. Treatment-emergent adverse events considered to be related to Kabiven or Perikabiven occurred in 21% and 15% of subjects, respectively. The most common adverse events reported in Kabiven-treated subjects were nausea (15%), pyrexia (9%), and hypertension (8%); hyperglycemia was reported in 2% and hypokalemia in 4%. The most common adverse events reported in Perikabiven-treated subjects were hyperglycemia (5%), hypokalemia (4%), and pyrexia (4%); nausea was noted in only 2%.

Injection site reactions were assessed using the modified Maddox score in Perikabiven-treated subjects receiving the product via peripheral vein. Six subjects developed a palpable venous cord greater than 3 inches above the IV site, and one subject experienced frank vein thrombosis.

Kabiven and Perikabiven contain soybean oil and egg phospholipid which may rarely cause allergic reactions. Cross-allergic reactions have been reported between soybean and peanut oil. For these reasons, foreign regulatory authorities have required that the product labels carry a contraindication for patients with hypersensitivity to egg, soy or peanut protein.

Device Considerations

The Center for Devices and Radiologic Health (CDRH), General Hospital Devices Branch, was consulted to evaluate device performance, biocompatibility and human factors.

Kabiven and Perikabiven are delivered using bags produced from [redacted] (b) (4) [redacted]. There were no deficiencies noted with regard to biocompatibility.

The following deficiencies, identified with regard to device performance and human factors, will need to be addressed before this application may be approved.

- **Device performance**

1. The applicant performed a test to demonstrate the resistance of the (b) (4) packaging to temperature, pressure and leakage, however it is unclear whether altitude was accounted for as part of the testing regimen. CDRH believes that it is more relevant to demonstrate the pressure at which the (b) (4) bag bursts. If the burst pressure significantly exceeds (for example, by a factor of 2) the typical atmospheric pressures expected with higher altitudes, then concerns of the bag bursting at these altitudes will have been mitigated. The applicant should repeat the testing regimen to determine burst pressure and utilize appropriate statistical methods to determine sample size and to interpret the test results.

(b) (4)

3. The applicant performed a test to demonstrate that the injection point does not leak when it is punctured by a 23 gauge needle. It appears that the septum at the injection point was punctured only once before subjecting the bag to a 20 kPa pressure. However, from the device description provided, it appears that one of the points is utilized to spike the bag with medication after the contents are mixed. It is conceivable that this septum would be penetrated multiple times prior to beginning the infusion. Also, it is unclear whether the 23 gauge needle will adequately test the non-coring nature of the septum at the injection point. Therefore the applicant should a) clarify whether the injection point could be penetrated multiple times, and if so, modify the test to account for multiple punctures, prior to testing the bag for leakage, and b) test the injection point leakage after the septum is punctured with a 19 or 21 gauge needle, needle gauges that are more representative of an extreme needle size for penetrating the injection point septum.

- **Human factors assessment**

Although the (b) (4) bag will only be utilized by health care providers, after evaluating the packaging sample provided, CDRH reviewers found it very cumbersome to manipulate. Thus, to ensure that use-related hazards associated with using the (b) (4) bag have been successfully identified and mitigated, the applicant should perform an assessment to identify potential use-related hazards and demonstrate that these hazards are no different than the usual hazards that clinicians face when delivering drug products through other IV bags. Based on this assessment, the applicant can then determine what human factors studies should be conducted, as outlined in CDRH's *Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, dated July 18, 2000.

When developing the appropriate human factors studies, consideration should be given to the following:

a. Devices and Labeling Used and Training Provided

The (b) (4) bags used in human factors studies should represent the final design and include instructions for use or any other labeling materials. The training provided to study participants should approximate the training that actual end users will receive. Participants should assess the clarity of the instructions for use and the applicant should assess the extent to which the instructions support safe and effective use of the (b) (4) bag. Study results demonstrating effectiveness of the training provided and instructions for use should be analyzed separately from the results of use performance.

b. User Tasks

The rationale for which user tasks will be included should be provided, and how many trials each participant would need to complete to adequately assess user performance. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

c. Use Environment and Conditions

Human factors studies should be conducted in an environment that includes or simulates all key aspects of the real-world environments in which (b) (4) bags would be used. Identification of potentially challenging use conditions should be anticipated, and use of the bags under such conditions should be evaluated. The applicant should describe the testing environment and realism of the simulated use and justify their appropriateness for use in human factors studies.

d. Study Participants

For devices that are intended to be marketed in the US, human factors studies should be conducted in the US with (American) English speaking participants. A minimum of 15 participants from each major user group should be tested. Participants should be representative of the intended end-user populations. If users with distinctly different characteristics (e.g., skill sets or experience levels) will use the bags, you should include 15 from each distinct group. A rationale that supports that these groups are representative of the overall population of users for the device should be provided. Participants should not be the applicant's own employees, or those that have been exposed to the device prior to the testing.

e. Data Collection

Data collected and analyzed in human factors studies should be described in terms of how they support the claim that the device can be used safely and effectively by the indicated users. Both empirical and qualitative data will be needed.

Empirical Data. Participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise

or critique from the test faciltator/moderator. Data regarding the successful or failed performance of key tasks should be measured directly rather than by soliciting participant opinions. Observation of participant behavior during the study will also permit assessment of participants' adherence to protocol and proper technique, and of any errors or problems that occur.

Qualitative Data. At the conclusion of the study, participants should be asked open-ended questions, such as, "Did you have any difficulty using this device?" "If so, can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Since the labeling and instructions for use are considered part of the user interface for the device, the questions should cover those components as well. The analysis of performance and subjective data should be directed toward understanding user performance and, particularly, task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

f. Protocol Review

CDRH offers to review human factors study protocols to ensure that the study(ies) align with published guidance.

Product Quality

Heavy metal content. The potential for heavy metal contamination of components in parenteral nutrition products during manufacturing exists. Although heavy metal content was monitored for individual drug substances per USP, there was no test acceptance criterion provided for the individual chambers or for the admixed final drug product. Since the volume of product administered is large ((b) (4) to 2556 mL per 24 hours), the potential exists for exposure to heavy metal levels that exceed daily allowable limits. In addition, patients receiving parenteral nutrition often have comorbidities (e.g., acid base imbalance, cardiac or pulmonary disease, renal or hepatic impairment) and may be less tolerant of higher-than-recommended heavy metal exposures if they exist.

On September 29, 2011, the applicant was requested to provide information for Kabiven and Perikabiven on the levels of chromium, manganese, arsenic, cadmium, lead, mercury, copper, selenium, and zinc in each chamber of the 3-chamber bag. Three batches each of drug product will need to be assessed.[2] In the complete response letter, the applicant will be further requested to control the daily intake of these metals by developing specifications and acceptance criteria for the levels of heavy metals contained in each chamber.

[2] On September 30, 2011, the Agency requested all manufacturers of total parenteral nutrition products to provide information on the levels of chromium, manganese, arsenic, cadmium, lead, mercury, copper, selenium, and zinc in three batches of each manufactured product. For multiple chamber products, the levels of these metals in each chamber would need to be reported. The manufacturers were also notified that the Agency had created a DARRTS Tracked Safety Issue to track the matter.

Stability. In correspondence dated November 01, 2011, the applicant described their ongoing stability program in which four of the nine pivotal batches demonstrated results above the acceptance limit for particulate matter. The applicant identified the particles present in the lipid chamber of the IV bag as (b) (4). The particles are thought to be caused by migration of components from the stopper. A teleconference was held on November 4, 2011 with Office of New Drug Quality Assessment (ONDQA) reviewers to discuss these findings.

Based on the data submitted to the NDA, an expiration dating period for the product has not been established. The Agency agreed that a (b) (4)-month expiration period may be acceptable if data from additional studies, including refrigerated conditions, support the period. The Agency also recommended that the stoppers be tested for (b) (4) levels and limits for (b) (4) content be added to the stopper specification, once an acceptable level is established. This data will need to be included in the applicant's resubmission.

Container/closure system. Although the proposed primary packaging material for the 3-chamber bag, (b) (4) the applicant must confirm that the (b) (4)

Inspection issues. The Office of Compliance has issued an overall "Withhold" recommendation for the application due to deficiencies identified during the inspection of the (b) (4). manufacturing facilities in (b) (4) and the Fresenius Kabi manufacturing facility in Sweden. Satisfactory resolution of these deficiencies is required before the application may be approved.

(b) (4) **drug substance.** The holder of DMF# (b) (4) (b) (4) will need to address deficiencies conveyed on August 31, 2011, involving the lack of adequate controls for unknown impurities in the (b) (4) drug substance that have been detected as a result of a change in manufacturing involving the starting material.

Pediatric Considerations

The Pediatric and Maternal Health Staff was consulted to assess the acceptability of the applicant's request that (b) (4)

In a letter dated September 8, 2011, the Agency informed the applicant that (b) (4)

[redacted]

Established and Tradename Reviews

ONDQA reviewers noted that the applicant's proposed established name "[redacted]" was not acceptable because it did not take into account all of the active substances present in the product. This finding was conveyed to the applicant via correspondence on June 17, 2011, and the established name "lipid injectable emulsion with amino acids and electrolytes and dextrose" was recommended.

The Division of Medication Error Prevention and Analysis (DMEPA) expressed concerns regarding the applicant's proposed proprietary names, "Kabiven" and "[redacted]." First, [redacted] should be avoided since one product should be administered by central vein only while the other product can be administered by peripheral or central vein. If the [redacted] "[redacted]" is unintentionally omitted, there is a risk that the wrong product could be administered via the wrong route. In addition, the [redacted] "[redacted]" is misleading since that product can be given centrally or peripherally, yet the name implies only "[redacted]" administration. For these reasons, DMEPA recommended the use of two unique proprietary names.

Following a conference call on September 2, 2011, the applicant withdrew the Kabiven and [redacted] tradenames. On September 7, 2011, the applicant submitted an amendment with new primary proposed proprietary names: "Kabiven" (for the product administered by the central venous route only) and "Perikabiven" or "[redacted]" (for the product administered by the peripheral or central venous routes). DMEPA has found the "Kabiven" and "Perikabiven" tradenames to be acceptable.

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/s/

JULIE G BEITZ
11/20/2011