

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200656Orig1s000

OTHER REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

From: Donna Snyder, MD, Medical Officer
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Pediatric and Maternal Health Staff (PMHS)

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drugs: Kabiven® and Perikabiven®

NDA: 200656

Applicant: Fresenius Kabi

Indication: Indicated for intravenous infusion as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition.

Materials Reviewed:

- PMHS consult review for Kabiven® and Perikabiven®, dated September 6, 2011, DARRTS Reference ID: 3008135
- PMHS consult review for Fluid Bundles (Dextrose and Saline), dated March 21, 2014, DARRTS Reference ID: 3472179
- PMHS consult request dated April 10, 2014, DARRTS Reference ID: 3487059
- Novamine 15%® labeling from Daily Med, accessed May 5, 2014, <http://dailymed.nlm.nih.gov>
- Intralipid® Emulsion labeling from Daily Med, accessed May 5, 2014, <http://dailymed.nlm.nih.gov>
- Aminosyn II® with electrolytes labeling from Daily Med, accessed May 5, 2014, <http://dailymed.nlm.nih.gov>
- Clinimix E® labeling from Daily Med, accessed May 5, 2014, <http://dailymed.nlm.nih.gov>

- Applicant’s submitted Pediatric Plan, dated October 21, 2011
- Proposed Kabiven® labeling dated March 25, 2014, from the applicant
- Proposed Perikabiven labeling® dated March 25, 2014, from the applicant

Consult Question: DGEIP requests advice on the proposed waiver and deferral of pediatric studies for the product under PREA and pediatric sections of labeling.

Background:

Kabiven® and Perikabiven® is a combination product developed to provide the basic components needed for parental nutrition: fat emulsion, glucose solution and amino acids solution with electrolytes. Kabiven® and Perikabiven® are not approved in the United States but are approved in over 60 countries worldwide. The table below includes the Reference Listed Drug (RLD) products for the fat and amino acid components of the product:

Drug Product	NDA or ANDA	Application Holder
Intralipid® 20% Injection	NDA 018449 and ANDA 020248	Fresenius
Novamine® 11.4% Injection	NDA 017957	Hospira
Clinimix® E Sulfite free with Electrolytes in Dextrose with Calcium	NDA 020678	Baxter Healthcare
Aminosyn® II with Electrolytes in Dextrose Injection with Calcium	NDA 019683	Hospira

Intralipid® is approved for all pediatric populations. Aminosyn® II is a hypertonic solution containing 20-25% dextrose and is not recommended for use in infants but may be used in older pediatric populations; however pediatric studies are not included in labeling. Novamine® 11.4% is no longer marketed in the United States and was withdrawn in June 2011. Novamine® 15% is the only concentration still marketed in the United States. Both Novamine® and Clinimix E® include general recommendations for pediatric use down to birth, but labeling states that the safety and effectiveness of the products in pediatric patients have not been established by adequate and well-controlled studies.

Kabiven® and Perikabiven® are labeled in the European Union for use in pediatric patients 2 years of age and older and carry a contraindication for use in pediatric patients under the age of 2 years of age because the product does not contain the amino acids cysteine and taurine which are considered to be essential in neonates and young infants.

Pediatric Review:

Under the Pediatric Research Equity Act (PREA), all applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must include a pediatric assessment that is adequate to assess the safety and effectiveness of the product and to support dosing and administration for all relevant pediatric populations, unless requirement is waived, deferred, or inapplicable. As a combination product, Kabiven® and Perikabiven® qualify as a new active ingredient.

With submission of the NDA, the applicant requested a waiver in pediatric patients less than 2 years of age (b) (4)

Discussion:

The criteria for a full or partial waiver under the Pediatric Research and Equity Act (PREA) are the following:

1. Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).
2. The product would be ineffective 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 labeling.
3. 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.

In addition, a partial waiver can be granted if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

Necessary studies are impossible or highly impracticable

The applicant did not request a waiver for this criterion. Since parenteral nutrition is widely used in pediatrics in many clinical settings where enteral feedings are not possible, studies in pediatrics should be feasible.¹ Thus, this criterion does not apply.

The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested

(b) (4)

¹ Kleinman, R. Pediatric Nutrition. American Academy of Pediatrics. Elk Grove, Illinois 60007-1098. 2014

² Soghier, L. and Brion, L. Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates. The Cochrane Collaboration. The Cochrane Library; 2006., Issue 4

³ Yarandi, S. et al. Amino acid composition in parenteral nutrition: what is the evidence? Curr Opin Clin Nutr Metab Care. 2011 January; 14(1): 75–82.

(b) (4)

PMHS suggests that a statement regarding the absence of cysteine and taurine be included in the pediatric use section.

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.

The applicant has submitted an argument that the Kabiven® and Perikabiven® do not provide a meaningful benefit over other available products on the market and has requested a waiver for pediatric patients less than 2 years of age. According to the applicant, there are 76 approved amino acid solutions, some of which are especially formulated for pediatric patients that may be a better choice for these patients.

However, according to ASPEN, in 2010, 132 of the 178 drug shortages were for parenteral nutrition components. Many of these drugs are in short supply because of manufacturing issues or because drug companies are no longer producing them.⁴ Currently, intravenous fat emulsions are listed on the FDA Current Drug Shortage Index.⁵ An additional product containing lipids as well as other parenteral nutrition components may fulfill an unmet need in pediatric patients.

⁴ ASPEN website, Drug Shortages Update.
https://www.nutritioncare.org/professional_resources/drug_shortages_update Accessed May 12, 2014.

⁵ Current Drug Shortages Index, FDA website.
<http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm> . Accessed May 12, 2014.

The current recommendations for pediatrics for parenteral nutrition are the following:
(From: Kleinman, R. Pediatric Nutrition, American Academy of Pediatrics. Elk Grove, Illinois 60007-1098. 2014).

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*Kleinman, R., Pediatric Nutrition, 7 Edition, pg. 573

Because this product contains lipid, protein (amino acids), and carbohydrates, and the requirements for these components differ by weight, this reviewer performed calculations to determine the utility of the product at several patient weights. Lipids are often infused for 12 hours rather than 24 hours to prevent hepatotoxicity⁶, especially in patients who are on long-term parenteral therapy. Calculations took into account both 12 and 24 hour infusions (see Appendix 1). For nearly all weight ranges, glucose would need to be supplemented. Overall, when infused over 12 hours, Kabiven® may be acceptable for pediatric patients down to 10 kg and Perikabiven® may be acceptable for pediatric patients down to 12 kg or the average weight of a 2 year old child.

Because use below in the younger and lower weight pediatric patients (less than 2 years of age or less than 12 kg for Perikabiven® and 10 kg for Kabiven®) would require the supplementation of protein (amino acids) **and** glucose in order to meet the nutritional needs of the patient, use of these products below these weights may be unlikely and may not provide a benefit over use of individual lipid, amino acid and electrolyte solutions. A partial waiver for this rationale may be reasonable.

PMHS recommends that the Division request that the applicant provide additional information to support a waiver for this rationale. 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.

⁶ Stout, M and Cober, P. Cyclic Parenteral Nutrition Infusion: Considerations for the Clinician. Nutrition Issues in Gastroenterology: Series 97, July 2011, pages 11-24.

Inability to make age-appropriate formulation:

This criterion does not apply since an intravenous formulation is acceptable for use in all pediatric populations.

Pediatric Use Labeling:

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

PMHS supplied labeling recommendations based on recently reviewed lipid and parenteral nutrition products. Intravenous fat emulsions (Intralipid®) include a boxed warning for a risk of death in neonates related to intravascular fat accumulation in the lungs. Intravenous fat emulsions also contain a warning for Parenteral Nutrition Associated Liver Disease. Dextrose bundles labeling recommends close monitoring in newborns, particularly premature and low birth weight infants, to avoid the risk of hypo- or hyperglycemia. Because Kabiven® and Perikabiven® will not be approved for use in pediatric patients, information otherwise should be limited to Section 8.4, Pediatric Use with appropriate cross-references to Warnings and Precautions for the specific risks identified for pediatric patients.

PMHS-PEDIATRIC TEAM RECOMMENDATIONS FOR LABELING

Note: Labeling below reflect labeling recommendations as of May 20, 2014. (See attached Appendices 2 and 3 with most recent versions of PMHS tracked changed suggestions to labeling).

See approval letter for final approved labeling.

WARNING: DEATH IN PRETERM INFANTS

See full prescribing information for complete boxed warning

- **Deaths in preterm infants have been reported in literature. (5.1, 8.4)**
- **Autopsy findings included intravascular fat accumulation in the lungs. (5.1, 8.4)**
- **Preterm and low birth weight infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion. (5.1, 8.4)**

HIGHLIGHTS OF PRESCRIBING INFORMATION

----- **WARNINGS AND PRECAUTIONS** -----

(b) (4)

-----**USE IN SPECIFIC POPULATIONS**-----

(b) (4)

1 INDICATIONS AND USAGE

(b) (4)

Limitations of Use:

(b) (4)

5 WARNINGS AND PRECAUTIONS

5.1 Death in Preterm Infants

Deaths in preterm infants after infusion of intravenous lipid emulsions have been reported. Autopsy findings included intravascular lipid accumulation in the lungs. Preterm and small for gestational age infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion. The safe and effective use of [KABIVEN/PERIKABIVEN] injection in pediatric patients, including preterm infants, has not been established.

(b) (4) Risk of Parenteral Nutrition Associated Liver Disease

Parenteral Nutrition Associated Liver Disease (PNALD) has been reported in patients who receive parenteral nutrition for extended periods of time, especially preterm infants, and can present as cholestasis or steatohepatitis¹. The exact etiology is unknown and is likely multifactorial. Intravenously administered phytosterols (plant sterols) contained in plant-derived lipid formulations have been associated with development of PNALD although a causal relationship has not been clearly established. If [KABIVEN/PERIKABIVEN] (b) (4) treated patients develop liver test abnormalities consider discontinuation or (b) (4) reduction.

8.4 Pediatric Use

Safety and effectiveness of [KABIVEN/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 (b) (4)*]. (b) (4)

(b) (4) Patients, including pediatric patients, may be at risk for PNALD [See (b) (4) *Warnings and Precautions (b) (4)*]. (b) (4)

(b) (4) does not contain the amino acids cysteine and taurine, (b) (4) considered essential (b) (4) 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 (b) (4) 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. (b) (4)

Discussion/Recommendations:

PMHS participated in several team meetings to discuss pediatric labeling and the potential approval of Kabiven® and Perikabiven®. PMHS agreed that the product triggered PREA as a new active ingredient and that a partial waiver for pediatric patients less than 2 years of age (b) (4) for Perikabiven® (b) (4) for Kabiven® 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) for which a waiver is being requested. PMHS recommends that DGIEP request additional information from the applicant to support a partial waiver. PMHS agrees (b) (4)

PMHS reminds DGIEP that PMHS and the Pediatric Review Committee (PeRC) are separate and distinct teams and that PMHS cannot make recommendations on behalf of the PeRC. However, the PeRC often provides recommendations that are consistent with advice provided by PMHS.

Appendix 1:

Calculations based on Maintenance Needs using Kabiven® and Perikabiven® for both 12 and 24 hour infusion of product

Perikabiven® contains 2.4 gr of protein (amino acids), 6.8 gr of glucose and 3.5 gr of fat per 100 mL

Kabiven® contains 3.3 gr of protein (amino acids), 9.8 gr of glucose and 3.9 gr of fat per 100 mL

Calculations include amount given if infused over 12 or 24 hours compared to total daily need as per AAP guidelines

5 kg infant Maintenance Fluids = 500 ml	Perikabiven®		Kabiven®		AAP Guidelines*
	24 hr	12 hr	24 hr	12 hr	
Protein	12 gr	6 gr	17 gr	8 gr	8-15 (1.5-3 gr/kg)
Glucose	34 gr	17 gr	49 gr	25 gr	50-150 (10-30 gr/kg)
Fat	18 gr	9 gr	20 gr	10 gr	2.5-15 gr (.5-3 gr/kg)
Fat/day (gr/kg)	3.6	1.8	4	2	

10 kg infant** Maintenance Fluids = 1000 ml	Perikabiven®		Kabiven®		AAP Guidelines*
	24 hr	12 hr	24 hr	12 hr	
Protein	24 gr	12 gr	33 gr	17	15-30 gr (1.5-3 gr/kg)
Glucose	68 gr	34 gr	98 gr	49	100-300 gr (10-30 gr/kg)
Fat	35 gr	18 gr	39 gr	20	5-30 gr (.5-3 kg/day)
Fat/day (gr/kg)	3.5	1.8	3.9	2	

**used recommendations for < 10 kg for this calculation to capture patients with weights up to 9.99 kg

12 kg infant Maintenance Fluids = 1100 ml	Perikabiven®		Kabiven®		AAP Guidelines*
	24 hr	12 hr	24 hr	12 hr	
Protein	26 gr	13 gr	36 gr	18 gr	12-30 gr (1- 2.5 gr/kg)
Glucose	75 gr	38 gr	108 gr	54 gr	96-336 (8-28 gr/kg)
Fat	39 gr	20 gr	43 gr	22 gr	12-36 (1-3 gr/kg)
Fat/day (gr/kg)	3.3	1.7	3.6	1.8	

14 kg infant Maintenance Fluids = 1200 ml	Perikabiven®		Kabiven®		AAP Guidelines*
	24 hr	12 hr	24 hr	12 hr	
Protein	29 gr	15 gr	40 gr	20 gr	14-35 gr (1- 2.5 gr/kg)
Glucose	82 gr	41 gr	118 gr	59 gr	112-392 (8-28 gr/kg)
Fat	42 gr	21 gr	47 gr	24 gr	14-42 (1-3 gr/kg)
Fat/day (gr/kg)	3.0	1.5	3.3	1.7	

20 kg infant§ Maintenance Fluids = 1500 ml	Perikabiven®		Kabiven®		AAP Guidelines*
	24 hr	12 hr	24 hr	12 hr	
Protein	36 gr	18 gr	50 gr	25 gr	20-50 gr (1 – 2.5 gr/kg)
Glucose	102 gr	51 gr	147 gr	74 gr	160-560 gr (8-28 gr/kg)
Fat	53 gr	27	59 gr	30 gr	20-60 gr (1-3 kg/day)
Fat/day (gr/kg)	2.7	1.4	3.0	1.5	

§used recommendations for 10 – 20 kg for this calculation to capture patients with weights up to 19.99 kg

30 kg infant Maintenance Fluids = 1700 ml	Perikabiven®		Kabiven®		AAP Guidelines*
	24 hr	12 hr	24 hr	12 hr	
Protein	41 gr	21 gr	56 gr	28 gr	24-60 gr (.8 – 2 gr/kg)
Glucose	116 gr	58 gr	167 gr	84 gr	150-600 gr (5-20 gr/kg)
Fat	60 gr	30 gr	66 gr	33 gr	30-90 gr (1-3 kg/day)
Fat/day (gr/kg)	2.0	1.0	2.2	1.1	

*Kleinman, R., Pediatric Nutrition, 7th Edition, pg. 573

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/s/

DONNA L SNYDER
05/21/2014

HARI C SACHS
05/21/2014
I agree with these recommendations

LYNNE P YAO
05/22/2014



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Pediatric and Maternal Health Staff Review

Date: May 6, 2014

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: KABIVEN & PERIKABIVEN (Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose) ^{(b) (4)}, for Intravenous Use

NDA: 200656

Subject: Labeling recommendations for subsections 8.1 and 8.3

Applicant: Fresenius Kabi USA, LLC

Materials Reviewed:

- November 25, 2015, Fresenius Kabi USA LLC, NDA submission
- August 19, 2013, PMHS-MHT, labeling review for Clinimix and Clinimix E
- September 10, 2013, PMHS-MHT, labeling review for ClinOlipid

Consult Question: DGIEP has request PMHS-MHT review labeling subsections 8.1 and 8.3

INTRODUCTION

On November 25, 2013, Fresenius Kabi USA, LLC submitted a Complete Response (CR) for Kabiven and Perikabiven (lipid injectable emulsion with amino acids, and electrolytes and dextrose), NDA 200656¹, in response to the CR Letter issued by the FDA on November 21, 2011, for clinical, product quality, device performance, human factors assessment and facility inspections deficiencies. Kabiven and Perikabiven are intended for use as supplements or as the sole source of nutrition in patients, providing macronutrients (carbohydrates, amino acids and lipids) and micronutrients (electrolytes) parenterally. These two products differ only in their glucose concentration. Kabiven contains (b) (4)% glucose and is intended for central infusion only. Perikabiven contains (b) (4)% glucose and can be administered via peripheral or central infusion. DGIEP consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the individual labeling for Kabiven and Perikabiven.

This review provides recommended revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

KABIVEN & PERIKABIVEN

Kabiven and Perikabiven are both a 3-chamber bag total parenteral nutrition system. These products (b) (4)

- KABIIVEN & PERIKABIVEN components
 - Chamber 1
 - Dextrose, USP in water for injection (the dextrose concentration differs between products)
 - Chamber 2
 - Solution of amino acids and electrolytes in water for injection and glacial acetic acid to adjust the pH so that the final solution has a pH of 5.4 to 5.8
 - Chamber 3
 - Intralipid[®] 20% (intravenous fat emulsion)
 - 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin and water for injection (in addition sodium hydroxide to adjust pH)

Total Parenteral Nutrition

Total Parenteral Nutrition (TPN) is prescribed for patients when they are unable to obtain calories or nutrition through oral intake. TPN typically consists of some or all of the following ingredients, carbohydrates, proteins, lipids, electrolytes, trace elements and insulin. The electrolytes often include sodium, potassium, chloride, phosphate, calcium citrate, bicarbonate, acetate and magnesium. Trace elements include copper, manganese, zinc, chromium and multi-vitamins.²

¹ PMHS-MHT notes that both products with separate tradenames and separate labeling are submitted under one NDA.

² Medline Plus. *Total Parenteral Nutrition*. (2013). Retrieved April 21, 2014, from <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601166.html>.

Total Parenteral Nutrition in Pregnancy

Nausea and vomiting are a very common side effects associated with pregnancy. Approximately, 85% of pregnant women will experience some nausea and vomiting during the first 3 months of pregnancy and 20% of those will continue to experience nausea and vomiting up to 5 months.³ Hyperemesis gravidarum is a severe type of nausea and vomiting that affects approximately 2% of pregnant women.³ Pregnant women with hyperemesis gravidarum are at risk for ketonuria, dehydration, and catabolism that may require hospitalization.⁴ In addition, severe dietary malnutrition during pregnancy has been shown to cause impairment of fetal growth and development.⁵ According to the American College of Obstetrics and Gynecology (ACOG), parenteral or enteral nutrition should be considered in patients with hyperemesis gravidarum who continue to lose weight after antiemetic therapy, and for patients who cannot tolerate oral liquids.⁶ Several case reports suggest that total parenteral nutrition is a good option for severely malnourished patients with hyperemesis gravidarum to maintain adequate nutrition and continue fetal growth, and for those who have seen a decrease of 10% or more in their pre-pregnancy body weight.^{7,8}

REVIEW OF DATA

Pregnancy

Animal reproduction studies have not been conducted with Kabiven or Perikabiven. A search of published literature was performed on the use of total parenteral nutrition during pregnancy and the most relevant case reports, articles and ACOG Clinical Management Guidelines for Nausea and Vomiting during pregnancy found are discussed below.

ACOG Practice Bulletin, Clinical Management Guidelines for Obstetricians-Gynecologists for Nausea and Vomiting of Pregnancy, Number 52, April 2004⁶

According to the American College of Obstetrics and Gynecology (ACOG), parenteral or enteral nutrition should be considered in patients with hyperemesis gravidarum who continue to lose weight after antiemetic therapy, and for patients who cannot tolerate oral liquids and are dehydrated. Additionally, vitamins including thiamine are recommended to be included with the parenteral nutrition when vomiting is present. ACOG as well as other authors recommend that a peripherally inserted catheter be used to avoid complications associated with a central catheter.⁹

³ Madjunkova, S., Maltepe, C., Koren, G. (2013). The Leading Concerns of American Women with Nausea and Vomiting of Pregnancy Calling Motherisk NVP Helpline. *Obstetrics and Gynecology International*, 2013, 1-7.

⁴ Tamay, A., Kuscus, N. (2011). Hyperemesis gravidarum: Current aspect. *Journal of Obstetrics and Gynecology*, 31:708-712.

⁵ Herbert, W., Seeds, J., Bowes, W., Sweeney, C. (1986). Fetal Growth Response to Total Parenteral Nutrition in Pregnancy: A Case Report. *The Journal of Reproductive Medicine*, 31(4), 263-266.

⁶ Nausea and vomiting of pregnancy. ACOG Practice Bulletin No. 52. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2004;103:803-15.

⁷ Peled, Y., Melamed, N., Hirsch, L., Hadar, E., Wiznitzer, A., Yogev, Y. (2013). Pregnancy Outcomes in Hyperemesis Gravidarum – The Role of Fetal Gender. *The Journal of Maternal-Fetal and Neonatal Medicine*.

⁸ Zibell-Frisk, D., Jen, KL., Rick, J. (1990). Use of parenteral nutrition to maintain adequate nutritional status in hyperemesis gravidarum. *Journal of Perinatology*, 10(4), 390-5. Abstract.

⁹ Russo-Stieglitz, KE., Levin, AB., Wagner, BA., Armenti, VT. (1999). Pregnancy Outcomes in patients requiring parenteral nutrition. *The Journal of Maternal-Fetal and Neonatal Medicine*, 8(4), 164-7.

Spiliopoulos, D., Spiliopoulos, M., Awala, A. (2013). Case Report: Esophageal Achalasia: An Uncommon Complication during pregnancy Treated Conservatively. Case Reports in Obstetrics and Gynecology, 2013.

A case report of a 39 year-old female who presented at 29 weeks gestation with vomiting, weight loss, dysphagia for solids and liquids with esophageal achalasia. The patient received peripheral total parenteral nutrition and delivered a healthy baby at 37 weeks gestation.

Herbert, W., Seeds, J., Bowes, W., Sweeney, C. (1986). Fetal Growth Response to Total Parenteral Nutrition in Pregnancy: A Case Report. The Journal of Reproductive Medicine, 31(4), 263-266.

A 19 year-old patient diagnosed at age 2 with lye ingestion and esophageal stricture presented initially at 8 weeks gestation. At this time her weight was unchanged from her pre-pregnancy weight. The patient was seen again at 26 weeks gestation with nausea, vomiting and diarrhea. The patient was admitted at 30 weeks gestation with vomiting, stomach pain and dehydration and decreased weight. The patient received TPN for 20 days when labor began at 34 weeks gestation and a healthy baby was delivered.

Russo-Stieglitz, K., Levine, A., Wagner, B., Armenti, V. (1999). Pregnancy Outcomes in Patients Requiring Parenteral Nutrition. The Journal of Maternal-Fetal Medicine, 8, 164-1697.

A retrospective review was conducted at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania, of the medical records of pregnant women who received parenteral nutrition from 1990-1997. In total, 26 pregnancies received parenteral nutrition via central catheters for reasons such as hyperemesis gravidarum, cholecystitis/pancreatitis, small bowel obstruction, intracranial bleed, ulcerative colitis and other. The parenteral nutrition consisted of dextrose, amino acids and lipids. Eleven of the pregnancies had 16 obstetric complications which included 2 cases of preeclampsia and 9 cases of preterm delivery (multiple gestation, cholecystitis, preeclampsia, pre-term rupture of membrane, history of re-current pre-term labor). In addition, there were two cases of idiopathic preterm labor in two of the pre-term labor patients. Also, a case of intrauterine growth retardation and one case of macrosomia. Five pregnancies of the 26 total ended in termination. Complications in 8 patients arose due to the central venous catheter (e.g., infection, thrombosis, occluded lines, pneumothorax and line dislodgment).

Lactation

The Drugs and Lactation Database (LactMed)¹⁰ was searched for available lactation data on with the use of Kabiven and Perikabiven and other parenteral nutrition products, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁰ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

Based on clinical practice guidelines and published literature, parenteral nutrition should be considered in cases of severe maternal malnutrition where nutritional requirements cannot be fulfilled by enteral intake because severe maternal malnutrition is associated with fetal risks and adverse pregnancy outcomes including preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality.

Information is lacking on the use of parenteral nutrition products during lactation. Lactation, unlike pregnancy, does not lead to complications like hyperemesis gravidarum. The applicant has not provided specific clinical situations in which woman breast feeding would require TPN. Therefore, PMHS-MHT is unable to comment on the likelihood of TPN use during breast feeding. However, because Kabiven and Perikabiven are not associated with clinically significant adverse reactions or tumorigenicity the appropriate regulatory statement for Nursing Mothers is, “caution should be exercised when (*name of drug*) is administered to a nursing woman”.¹¹

CONCLUSION

A Pregnancy Category C¹² classification is appropriate for both Kabiven and Perikabiven labeling based on the lack of adequate and well controlled studies in pregnant women and a lack of animal reproduction studies.

The pregnancy subsection of the labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of labeling was revised to comply with current labeling recommendations.

¹¹ 21CFR201.57

¹² Pregnancy Category C definition: Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, or animal studies have not been conducted and there are no adequate and well controlled studies in humans.

PMHS-MHT discussed our labeling recommendations with DGIEP at a meeting on May 1, 2014. PMHS-MHT recommendations are below and reflect the discussions with the Division at that meeting. PMHS-MHT refers to the final NDA action for final labeling.

PMHS LABELING RECOMMENDATIONS

KABIVEN

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate or well-controlled studies in pregnant women with Kabiven. Additionally, animal reproduction studies have not been conducted with lipid injectable emulsion with amino acids and electrolytes and dextrose. It is not known whether Kabiven can cause fetal harm when administered to a pregnant woman in women. Kabiven should be given to a pregnant woman only if clearly needed.

Clinical Considerations

Based on clinical practice guidelines, parenteral nutrition should be considered in cases of severe maternal malnutrition where nutritional requirements cannot be fulfilled by enteral intake because of the risks to the fetus associated with severe malnutrition, such as preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality.

8.3 Nursing Mothers

It is not known whether Kabiven is present in human milk. Because many drugs are present in human milk, caution should be exercised when Kabiven is administered to a nursing woman.

PERIKABIVEN

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate or well-controlled studies in pregnant women with Perikabiven. Additionally, animal reproduction studies have not been conducted with lipid injectable emulsion with amino acids and electrolytes and dextrose. It is not known whether Perikabiven can cause fetal harm when administered to a pregnant woman. Perikabiven should be given to a pregnant woman only if clearly needed.

Clinical Considerations

Based on clinical practice guidelines, parenteral nutrition should be considered in cases of severe maternal malnutrition where nutritional requirements cannot be fulfilled by enteral intake because of the risks to the fetus associated with severe malnutrition, such as preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality.

8.3 Nursing Mothers

It is not known whether PERIKABIVEN is present in human milk. Because many drugs are present in human milk, caution should be exercised when PERIKABIVEN is administered to a nursing woman.

Appendix A

Sponsor's Labeling Recommendations



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/s/

CARRIE M CERESA
05/06/2014

JEANINE A BEST
05/06/2014

LYNNE P YAO
05/13/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: April 30, 2014

To: Matthew Brancazio, Pharm D
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 200656
OPDP Comments for draft Kabiven and Perikabiven (Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose) draft PI

OPDP has reviewed the proposed draft PI for Kabiven and Perikabiven (Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose). We have reviewed the draft PI, retrieved from Sharepoint on April 29, 2014, and have the following comments.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
04/30/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review

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

DATE: April 15, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Mathew Brancazio, Regulatory Project Manager, CDER/OND/ODEIII/DGIEP

SUBJECT: **NDA 200656 (Part of Resubmission Dated 3/25/2014)**
Applicant: Fresenius Kabi (FK)
Device Constituent: Parenteral Nutritional Bags
Drug Constituent: Kabiven/PeriKabiven
Intended Treatment: total parenteral nutrition
CDRH CTS Tracking No.: ICC 1400190

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Combination Product Device Information

NDA 200656

Applicant: Fresenius Kabi (FK)

Device Constituent: Parenteral Nutritional Bags

Drug Constituent: Kabiven/PeriKabiven

Intended Treatment: total parenteral nutrition

CDRH Human Factors Involvement History with the Current Submission

- 3/25/2014 – CDRH HF was requested to review the human factors validation study reports included in the NDA. Class 2 resubmission of NDA 200656 following complete response issuance (11/21/11). FK has submitted the results of their HF study, the protocols were previously reviewed by CDRH HF
EDR Location: <\\CDSESUB1\evsprod\NDA200656\0030>
<\\CDSESUB1\evsprod\NDA200656\0030\m1\us\cover-letter-nda-200656.pdf>
- 4/17/2014 – CDRH HF provided review recommendation. CDRH HF found the study results to be acceptable.

Overview and Recommendation

The Division of Gastroenterology and Inborn Errors Products requested a consultative review from CDRH Human Factors team to review two human factors validation study reports contained in the NDA.

The Applicant seeks FDA's approval for the Kabiven and PeriKabiven Triple chamber (b) (4) Bag that contains different parenteral nutrients in their NDA resubmission dated June 1, 2012. CDRH Human Factors team was originally consulted in February 2012 to review the Human Factors protocol, which resulted in eight deficiencies that were issued to APP. A revised protocol based on the comments and responses to each comment were provided for review on April 02, 2012 and CDRH confirmed on April 10, 2012 that the study as drafted was sufficient to address concerns. As a result, APP conducted the study in April 2012. This study was initially intended to be the final Human Factors/usability validation study. However, this study showed relative high failure rates on task performance, which indicated that changes to product designs/instruction for use/training were necessary to demonstrate that the proposed product can be used safely and effectively. Subsequently, APP conducted a labeling focus group study in May 2012. This study demonstrated that additional changes to the bag label were necessary to ensure that it can be understood by intended users.

On June 1, 2012, Fresenius submitted their complete response resubmission; however, the Division subsequently determined that this resubmission was incomplete because a final human factors study had not yet been completed and submitted to the NDA. On July 26, 2012, the Division issued a letter providing additional advice to Fresenius on their planned "summative" study (as well as comments on the Device performance).

On August 24, 2012, the Applicant submitted the revised HF study protocol along with their response to the deficiencies for Agency review. At this time, the revised protocol and Sponsor's response appears adequate with one exception. The review recommends that the task of rolling the bag be included as part of the tasks to be tested the study. FDA issued an advice letter on September 14, 2012.

The Sponsor conducted the final human factors/usability study and the results were discussed with the Division during an industry meeting held on December 11, 2012. However, the results of this study did not support the conclusion of safe use. Based on the discussion and comments received in December 2012, Fresenius states that they have made every attempt to mitigate errors observed in the previous study and have enhanced usability of the 3 chamber bag to ensure improved patient safety.

Subsequently, the Sponsor submitted type C meeting request, which was held in September 25, 2013. The meeting package contains results the requested human factors assessment that the Sponsor would like to discuss and gain agreement on the re-submission of the complete response to the NDA. That study showed that nurses could use the product safely and effectively without training. A few errors occurred in the pharmacist and pharmacy technician cohorts with regard to partial activation and the use of the injection port for additions. The Sponsor stated that the errors that occurred could not be further mitigated by design changes. FK proposed training as an additional measure to further mitigate these errors. The Sponsor proposed a more focused validation study that will include training of the study participants. In addition, FDA indicated that since this product may be used in the homecare setting, we request you conduct a validation study that includes nurses, homecare providers, and homecare patients.

The validation study should evaluate 3 objectives: 1) Ability for nurses to self-train, 2) Effectiveness of training homecare users on use of the product, and 3) Performance of the tasks specific to activation and administration of the product. In March 25, 2014, 2013, the Sponsor submitted the results of their recent human factors validation studies.

This consultant found the results of the studies acceptable. The consultant has one advice that can be communicated to the Sponsor after CDER's concurrence:

Your human factors training validation study shows that training is an effective mitigation to reduce use errors associated with your 3-chamber parenteral nutritional bag. Your human factors study with homecare nurses underscored the effectiveness of this mitigation. While we accepted the results of both studies, we ask that you specify training as a requirement in your Instructions for Use and other device labeling, and ensure that the in-service training guide will be used consistently in your training program.

Appendix 1: CDRH Human Factors Review

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.

Appendix 2: Device Related Information

(b) (4)



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/s/

MATTHEW B BRANCAZIO
04/22/2014
administratively entered for CDRH reviewer

HUMAN FACTORS STUDY PROTOCOL REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review: April 14, 2014

Requesting Office or Division: Office of Gastroenterology and Inborn Errors Products (DGIEP)

Application Type and Number: NDA 200656

Product Name and Strength: Kabiven and Perikabiven (Lipid Injectable Emulsion with Amino Acids and electrolytes and Dextrose) (b) (4)
1026 mL, 1440 mL, 1540 mL, 1920 mL, 2053 mL,
2566 mL, 2400 mL

Product Type: Multi-ingredient Product

Rx or OTC: Prescription

Applicant/Sponsor Name: APP Pharmaceuticals

Submission Date: March 25, 2014

OSE RCM #: 2013-2783

DMEPA Primary Reviewer: Denise V. Baugh, PharmD, BCPS

DMEPA Associate Director: Lubna Merchant, PharmD, M.S.

1 REASON FOR REVIEW

This review responds to a request from DGIEP to evaluate the Human Factor Study results, revised prescribing information and container labels provided by the Applicant in the resubmission to the Complete Response dated November 22, 2013 for Kabiven and Perikabiven (NDA 200656).

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A and F
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant submitted the results of a supplemental summative study involving trained pharmacists and pharmacy technicians as requested by the agency. DMEPA found the study design acceptable and no use errors or close calls were observed during the study. The Applicant has adequately addressed the failures cited in our previous review (OSE Review # 2012-937 dated July 20, 2012). Additionally, we note that although it is unlikely that all pharmacy staff will receive the training as was given in this study (due to absences or time constraints), it is also unlikely that new parenteral nutrition products would be introduced into this clinical setting without staff having access to the training material necessary to support the safe use of the product.

The Applicant also submitted the results of a summative study involving self-trained home care nurses as it is recognized that the home is a setting where this product may be given. One participant in this study did not fully activate the bag (i.e., parts of the vertical seal between the lipid and amino acid chambers remained closed) and this error was attributed to the user.

Specifically, the Applicant states that the participant did not appear to read the IFU, the illustrated user guide, and was distracted while the training video was playing.

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.

4 CONCLUSION & RECOMMENDATIONS

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.

APPENDICES

Appendix A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kabiven and Perikabiven that APP Pharmaceuticals submitted on November 25, 2013.

Table 2. Relevant Product Information for Kabiven and Perikabiven	
Active Ingredient	lipid injectable emulsion with amino acids and electrolytes and dextrose
Indication	(b) (4)
Route of Administration	Intravenous infusion into peripheral or central vein (Perikabiven), or central vein only (Kabiven)
Dosage Form	(b) (4)
Strength	Dextrose, amino acids, electrolytes and fat emulsion
Dose and Frequency	Individualized and dependent on the patient's clinical condition, body weight and nutritional requirement
How Supplied	Three chamber bag including Glucose solution (Chamber 1), Amino Acid Solution (Chamber 2) and Lipid Emulsion (Chamber 3) with total volumes after mixing of 1026 mL, 1440 mL, 1540 mL, 1920 mL, 2053 mL, 2400 mL, and 2566 mL per bag
Storage	Allows refrigeration of product for twenty-four hours at 2°C to 8°C/36°F to 46°F, and after breaking the vertical seals, chemical and physical in-use stability of the mixed three chamber bag has been demonstrated for twenty-four hours for infusion at room temperature (25°C/77°F). Exposure to heat should be minimized and product should be protected from freezing. If frozen, the bag should be discarded. Product should be used immediately after mixing and when additions have been made. If not used immediately, the in-use storage time and conditions prior to use should normally not be stored longer than twenty-four hours at 2°C to 8°C /36°F to 46°F. After removal from storage, the admixture should be infused within twenty-four hours

Appendix C. PREVIOUS DMEPA REVIEWS

DMEPA evaluated the protocol submitted June 1, 2012 (OSE Review # 2012-937 dated July 20, 2012) and concluded that the protocol required revision before further testing occurred. DMEPA recommended that the Applicant evaluate if the bag was rolled correctly, if participants can identify a partially mixed bag, and ensure participants properly agitate the bag after activation. Additionally, we had comments regarding the product design.

Appendix D. HUMAN FACTORS STUDY RESULTS AND PROTOCOL

The Applicant submitted study results for 2 separate cohorts. One study (which was supplemental) was conducted using trained pharmacists and pharmacy technicians and the second one involved self-trained home care nurses. The following is a summary of each study respectively:

Training Usability Study Involving Trained pharmacists/pharmacy technicians

Study objective – validate that the training provided by the sponsor is effective in mitigating use errors

Participants – 8 pharmacists and 7 pharmacy technicians in a simulated clinical environment

Training – training consisted of watching a 5 minute instructional video, followed by a live demonstration on the use of the product by the trainer and ending with a hands-on skills lab. There was a 24 hour lag time between the training and the task evaluation. This was representative of the proposed training the sponsor will provide at institutions where the product is used; training sessions were no longer than 30 minutes with 1 to 4 participants per session; facilitator observed performance throughout the study without assisting the participant.

Tasks – choosing the bag, inspecting the bag, removing the over pouch, activating the bag, and injecting the additives

Data Collection – pass or fail criteria; no close calls were observed in the study; participants were asked to provide comments regarding any safety concerns and asked questions regarding the usability of the product.

Home Care Usability Study involving Self-Trained Home Care Nurses

Study Objective – demonstrate that instructional materials are sufficient to provide home care nurses with the knowledge and ability to train a patient to use the products in a home setting

Participants – 15 nurses who have routinely trained home care patients or caregivers to use parenteral nutrition.

Training – materials available for self-training will include instructions for use, prescribing information, on-bag label, materials available on website (training video, user manual technical assistance number)

Tasks – inspection of the bag, activation, making additions, spiking for infusion; all tasks will be performed once by each participant


Data Collection – pass or fail criteria; if the facilitators observe the study participants experiencing confusion, misinterpretation, difficulty, or error in demonstrating how to prepare the bag that would result in mistreatment or harm, but the user recovers and no actual performance failure occurs, this will be noted as a close call. All close calls were assessed for their root cause.

APPENDIX F. Content of Ingredients for Kabiven and Perikabiven

Content of Ingredients for Kabiven

How Supplied	2566 mL	2053 mL	1540 mL	1026 mL
				(b) (4)
				(b) (4)
Composition				
Soybean Oil, USP (g/100 mL)			3.9	
Dextrose (b) (4) USP (g/100 mL)			9.8	
Amino Acids, USP (g/100 mL)			3.31	
Total Nitrogen (mg/100 mL)			526	
Essential amino acids (mg/100 mL)	Leucine, USP		231	
	Isoleucine, USP		164	
	Valine, USP		213	
	Lysine, USP (added as the hydrochloride salt)		263	
	Phenylalanine, USP		231	
	Threonine, USP		164	
	Methionine, USP		164	
	Tryptophan, USP		55	
Nonessential amino acids (mg/100 mL)	Alanine, USP		467	
	Arginine, USP		330	
	Aspartic Acid, USP		99	
	Glutamic Acid		164	
	Glycine, USP		231	
	Histidine, USP		199	
	Proline, USP		199	
	Serine, USP		131	
	Tyrosine, USP		6.7	
Electrolytes (mg/100 mL)	Sodium Acetate Trihydrate, USP		239	
	Potassium Chloride, USP		174	
	Sodium Glycerophosphate Anhydrous		147	
	Magnesium (b) (4) Heptahydrate, USP		96	
	Calcium Chloride Dihydrate, USP		29	
Electrolyte Profile (mEq/L)	Sodium ²		31 (31 mmol/L)	
	Potassium		23 (23 mmol/L)	
	Magnesium		7.8 (3.9 mmol/L)	
	Calcium		3.8 (1.9 mmol/L)	
	Phosphorous ³		N.A. (9.7 mmol/L)	
	Acetate ⁴		38 (38 mmol/L)	
	Chloride ⁵		45 (45 mmol/L)	
	(b) (4)		7.8 (3.9 mmol/L)	
Caloric Content (kcal/L)	From Dextrose		330	
	From Lipid		(b) (4)	
	From Amino Acids		130	
	Total		(b) (4)	
pH ⁷			5.6	
Osmolarity (mOsm/L)			1060	


Dosage and Administration for Kabiven

- Adult dosage: 19 to 38 mL/kg/day (0.63 to 1.26 g/kg/day of amino acids, 0.74 to 1.48 g/kg/day of fat, 1.85 to 3.71 g/kg/day of dextrose) (2)
-  (b) (4)
- The maximum infusion rate is 2.6 mL/kg/hour (corresponding to 0.25 g/kg/hour of dextrose, the limiting factor, 0.09 g/kg/h of amino acids, and 0.1 g/kg/hour of fat). Recommended infusion period is 12 to 24 hours (2)

Content of Ingredients for Perikabiven

	2400 mL	1920 mL	1440 mL
How Supplied	(b) (4)		
(b) (4)			
Composition			
Soybean Oil, USP (g/100 mL)		3.5	
Dextrose (b) (4) USP (g/100 mL)		6.8	
Amino Acids, USP (g/100 mL)		2.36	
Total Nitrogen (mg/100 mL)		375	
Essential amino acids (mg/100 mL)	Leucine, USP	164	
	Isoleucine, USP	116	
	Valine, USP	152	
	Lysine, USP (added as the hydrochloride salt)	187	
	Phenylalanine, USP	164	
	Threonine, USP	116	
	Methionine, USP	116	
	Tryptophan, USP	40	
Nonessential amino acids (mg/100 mL)	Alanine, USP	333	
	Arginine, USP	235	
	Aspartic Acid, USP	71	
	Glutamic Acid	116	
	Glycine, USP	164	
	Histidine, USP	141	
	Proline, USP	141	
	Serine, USP	94	
	Tyrosine, USP	4.8	
Electrolytes (mg/100 mL)	Sodium Acetate Trihydrate, USP	170	
	Potassium Chloride, USP	124	
	Sodium Glycerophosphate Anhydrous	105	
	Magnesium (b) (4) Heptahydrate, USP	68	
	Calcium Chloride Dihydrate, USP	20	
Electrolyte Profile ¹ (mEq/L)	Sodium ²	22 (22 mmol/L)	
	Potassium	17 (17 mmol/L)	
	Magnesium	5.6 (2.8 mmol/L)	
	Calcium	2.8 (1.4 mmol/L)	
	Phosphorous ³	N.A. (7.5 mmol/L)	
	Acetate ⁴	27 (27 mmol/L)	
	Chloride ⁵	32 (32 mmol/L)	
	(b) (4)	5.6 (2.8 mmol/L)	
Caloric Content (kcal/L)	From Dextrose	230	
	From Lipid	(b) (4)	
	From Amino Acids	95	
	Total	(b) (4)	
pH ⁷	5.6		
Osmolarity (mOsm/L)	750		

Dosage and Administration for Perikabiven

- Adult dosage: 27 to 40 mL/kg/day (0.64 to 0.94g/kg/day of amino acids, 0.95 to 1.4 g/kg/day of fat, 1.83 to 2.71 g/kg/day of dextrose) (2)
-  (b) (4)
- The maximum infusion rate is 3.7 mL/kg/h (corresponding to 0.25 g/kg/h of dextrose, the limiting factor, 0.09 g/kg/h of amino acids, 0.13 g/kg/h fat). The recommended infusion period is 12 to 24 hours (2)

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/s/

DENISE V BAUGH
04/14/2014

LUBNA A MERCHANT
04/14/2014



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: December 6, 2013

From: CDR Alan Stevens, Mechanical and Reliability Engineering
CDRH/ODE/DAGID/General Hospital Devices Branch (GHDB)

To: Matthew Brancazio, Senior Program Manager
CDER/OND/ODEIII/DGIEP

Subject: CDRH Engineering Consult, NDA 200656, (b) (4) APP Pharmaceuticals
(Multi-Chamber IV Bag to store, mix and dispense Kabiven and (b) (4))

Summary: This review focuses on resolving device engineering deficiencies for leaking, burst, dropping, and infusion port leaking. The documents reviewed are from the sponsor's November 22, 2013 submission. A complete review of the additional data demonstrates that the engineering deficiencies have been adequately resolved.

No additional device engineering deficiencies remain.

1. **Issue**

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 200656. The device constituent of this combination product consists of a Multi Chamber Plastic IV Bag for the delivery of Kabiven and (b) (4).

Prior consults were provided, dated August 26, 2011 and July 19, 2012.

This supplemental consult will address the remaining device engineering deficiencies, which include burst pressure tests, drop tests, and injection septum seal tests.

NOTE: For completeness, information from the prior reviews remains within this document. New review is in bold font.

2. **Device Description**

The Kabiven and (b) (4) is packaged in a flexible three chamber bag called the (b) (4) packaging system. This system has been developed by the company, Fresenius Kabi. The packaging system is depicted in Figure 1a below.

The primary bag is produced from (b) (4)

(b) (4)
The cap

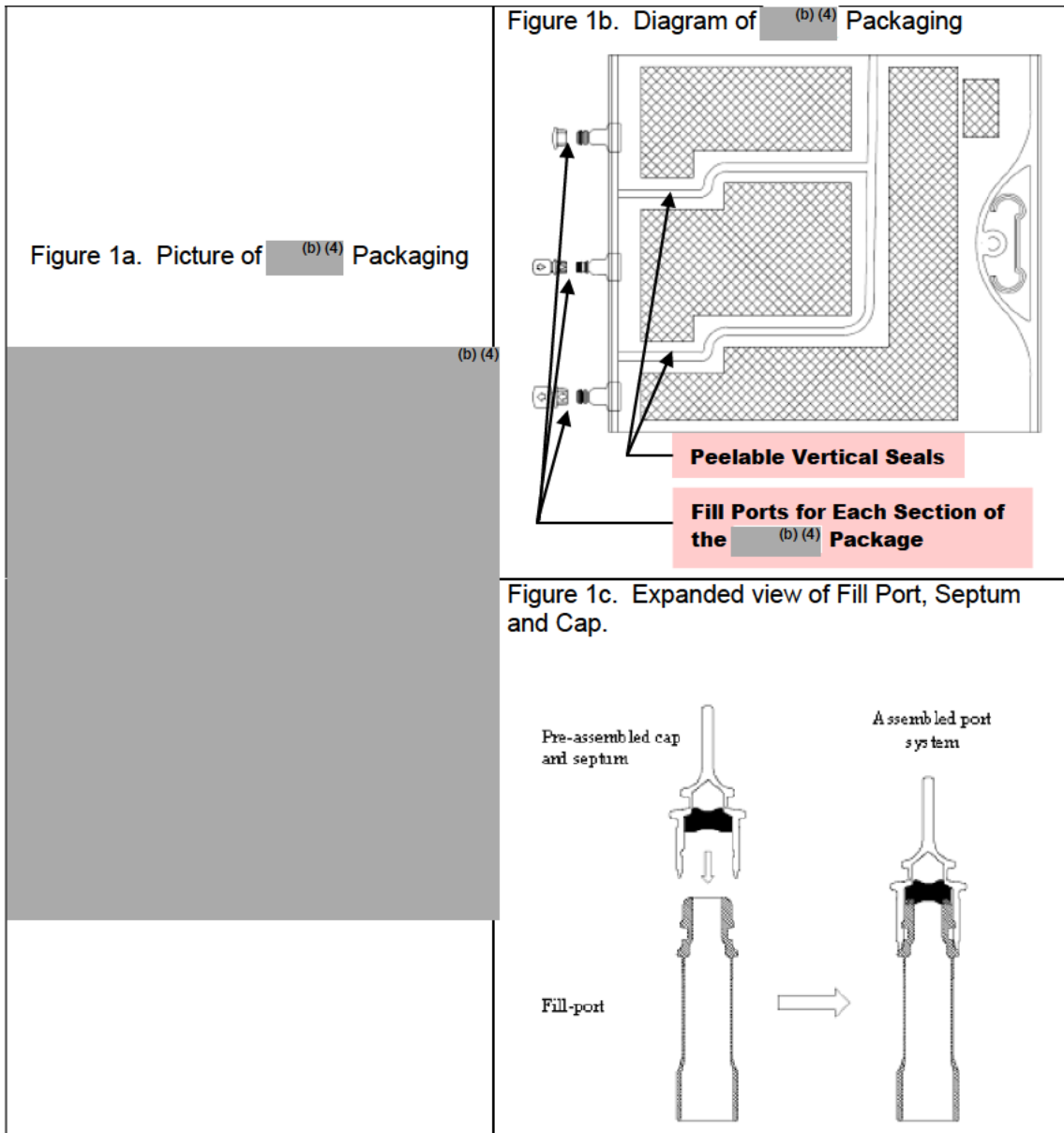
NDA 200656, (b) (4)

APP Pharmaceuticals

(Multi-Chamber IV Bag to store, mix and dispense Kabiven and (b) (4))

is not in direct contact with the infusion solutions. One of the ports is used for making injections to the bag after mixing, another port is used for infusion through an infusion set with an infusion spike and the third port is a blind port, used only for filling the bag.

Figure 1. Picture and Diagram of (b) (4) Packaging



3. Documents Reviewed

December 6, 2013, CDRH Review

EDR Location: <\\CDSESUB1\evsprod\NDA200656\200656.enx>

Supporting Document Number: 27

eCTD Sequence Number: 0025

- Infusion stopper report, 217940
- Packaging material study, 215990

July 19, 2012 CDRH Review

June 1, 2012 Complete Response Letter an/d attachments.

August 16, 2011 CDRH Review

NDA 200656 – Original Submission (Dated January 28, 2011) and Subsequent Amendments

Amendment 1 – Dated March 10, 2011

Amendment 2 – Dated April 6, 2011

Amendment 3 – Dated April 25, 2011

Amendment 4 – Dated May 10, 2011

Amendment 5 – Dated June 17, 2011

Amendment 6 – Dated July 7, 2011

Amendment 7 – Dated July 27, 2011

Amendment 8 – Dated July 27, 2011

Amendment 9 – Dated August 5, 2011

ISO 15747 “Plastic containers for intravenous injection”

D IN 58363 “Infusion containers and accessories.” Part 15 “Infusion bags and bottles made of plastic. Requirements and testing.”

4. CDRH Review and Comments

CDRH’s Review of the device constituent for this Combination Product consisted of an assessment of Device Performance, Human Factors, and Biocompatibility.

CDRH did not review (b) (4) because this aspect of the device is being reviewed by CDER. This device does not contain Electrical and/or Software Components.

General

The (b) (4) packaging bag would typically be considered to be a primary container / closure for the Kabiven and (b) (4) drug product, if it were a single chamber IV bag. However, given that there are multiple chambers, and multiple steps that the user must take to manipulate the bag in order to prepare the drug product (i.e. remove the seals separating each chamber, mix the contents to achieve a homogeneous solution, etc.). As a result, CDRH is providing this consult to express our questions and concerns regarding the (b) (4) packaging.

Functional / Mechanical Testing

In addition to CDRH’s prior deficiencies regarding leakage, burst, and drop testing. An additional cause of leaking due to puncturing the infusion port multiple times has been identified. The sponsor provided a report titled, “Integrity of the infusion stopper using additions with a needle (doc. No. 217940/2).

Test Methodology:

Ten containers are tested using a new hypodermic needle with an external diameter of 0.8 mm (21G), 40 mm length, used for each container. Each infusion stopper is pierced 10 times with the needle, each time at a different site. Integrity is tested, by then subjecting the container to an internal overpressure of 27 kPa, for 10 minutes. The containers are then spiked at the insertion point (spike port) with IV spike set according to ISO 8356-4 (Transcodan B/S86). The bags are then hung on an IV pole for 5 hours with the spike sets remaining in the infusion port.

The test conditions, sample sizes and acceptance criteria were chosen based on recommendations in the (b) (4)

(b) (4) or ISO 15747:2010, Plastic containers for intravenous injections.

Acceptance Criteria:

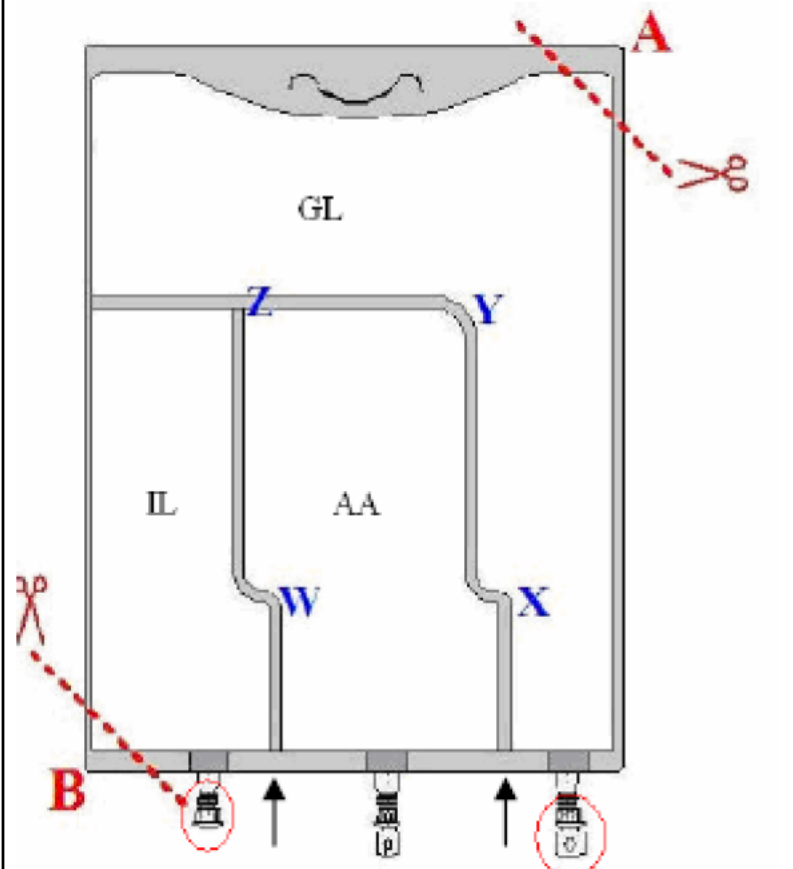
Integrity of Stopper: No leakage

Fragmentation: (b) (4) **Particle count does not exceed** (b) (4)

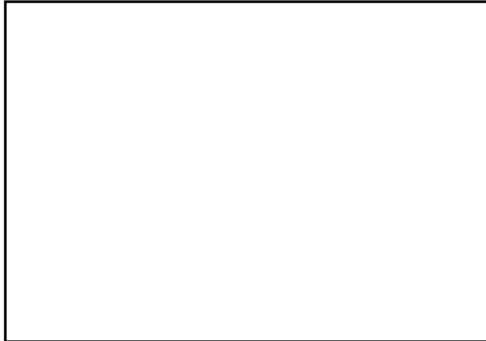
Results: No leakage and zero particles were observed.

CDRH Review: The testing adequately demonstrates that infusion port is capable of withstanding multiple punctures should a user inject through this port, rather than the intended injection port. The response is adequate.

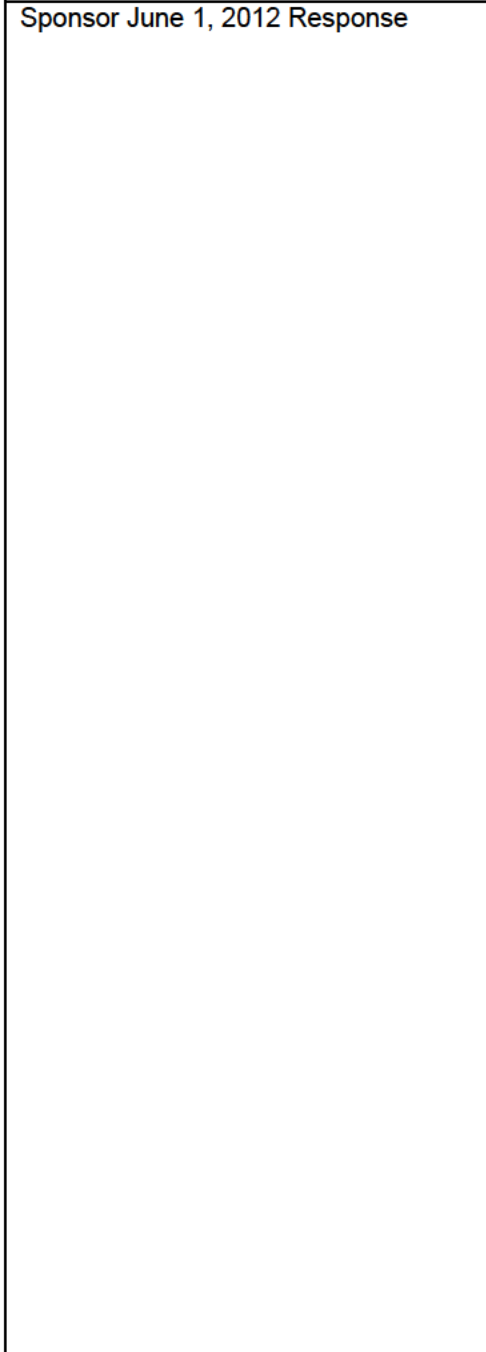
<p>CDRH August 16, 2011 Deficiency</p>	<p><i>The Sponsor performed a test to demonstrate the (b) (4) packaging's resistance to temperature, pressure and leakage, per the recommendations within ISO 15747 and D IN 58363-15. Based on the description of the test within these standards, it is unclear whether altitude was accounted for as part of testing regimen. For instance, the Sponsor's test states that the (b) (4) bag is conditioned for 24 hours at a temperature of 50 +/- 5 Deg. C. The bag is then exposed to a pressure of 500 mbar (50 kPa) for 15 seconds. The bag is considered to pass the test if it does not leak any fluids. Our concern is that atmospheric pressure changes significantly with altitude (for example, the typical atmospheric pressure in Denver, Colorado, which is approximately 1 mile above sea level, is approximately 85 kPa). Given the difference in pressure based on varying altitude, temperature and humidity, we believe that it is more relevant to demonstrate the pressure at which the (b) (4) bag bursts. If the burst pressure significantly exceeds (factor of 2x) the typical change in atmospheric pressure as it relates to altitude, then our concerns of the bag bursting due to this environmental change will have been mitigated. The Sponsor should utilize a statistically significant sample size when performing this test. The Sponsor should use basic statistical analyses when interpreting the test results.</i></p>
<p>Sponsor June 1, 2012 Response</p>	<p>In order to address FDA's request additional studies have been performed to evaluate effects at higher altitudes and to determine the burst pressure. Please refer to SECTION 3.2.P.7 BURST PRESSURE DETERMINATION for study design and rationale, testing methods, and results. If the three chamber bag were to be transported to higher altitudes and hence lower atmospheric pressure, the only effect within the bag that potentially could cause higher pressure is the increase in the head space volume. It was demonstrated that an increase in head space volume by 4-fold, simulating a height of 10,000 m, would only result in minor changes in internal pressure, i.e. an increase of 1.4 kPa. The measured increase in pressure at which the bags were seen to burst was between 60-70kPa. Therefore the burst pressure is significantly higher, by a factor of approx 40-X the pressures that are expected to be observed at very high altitudes of approximately 10,000m.</p>
<p>CDRH Review of June 1, 2012 Response</p>	<p>The sponsor provided two separate tests to demonstrate material strength under pressure. In each test, the inner seals were opened prior to undergoing stress testing. The sponsor references altitude changes during shipping (e.g. transport by airplane) and relies on the anecdotal evidence of shipping 500 pallets with no reported problems. The issue of altitude changes is most likely not a hazard once the seals are broken because at</p>

	<p>that point the product is in use and the pressure will have equilibrated. The validity of the acceptance criteria was the fundamental concern of the prior deficiency. The new information does not adequately address these concerns. Please demonstrate that the strength of the inner seals is sufficiently robust to prevent the premature opening of the seals. The prior question requested statistically significant data. The response did not appear to identify any statistically based justification for the use of 10 samples. Please identify the confidence and reliability level (e.g. 95/95) used to select the sample size and describe why that level is acceptable.</p>
<p>Sponsor November 22, 2013 Response</p>	<p>The sponsor addresses this deficiency in the packaging material study report, #215990.</p> <p>As shown in the diagram below, the test method was to pressurize the bag from position A and record the burst pressures of the seals using pressure gages inserted at the ports.</p> 
<p>CDRH Review of November 22, 2013 Response</p>	<p>The testing demonstrates that the burst pressure exceeds by a factor of 4 the expected. The response has adequately addressed the deficiency.</p>

CDRH August 16, 2011 Deficiency (b) (4)



Sponsor June 1, 2012 Response



(b) (4)

	(b) (4)
CDRH Review of June 1, 2012 Response	The response indicates that the objective of the drop testing is not to assure that foreseeable hazards associated with use have been mitigated, but to identify weaknesses during development and production. FDA is interested in reviewing data to demonstrate that foreseeable hazards have been mitigated such that any remaining risks are reasonably low. Please provide drop testing data simulating conditions of foreseeable use (e.g. dropping from the height at which the bag would be hung). Tests should use minimum and maximum fill volumes and should include statistically based sample size based on a justified confidence / reliability level.
Sponsor's November 22, 2013 Response	Drop tests were performed from a height that is representative of the typical height from which the user will hang the bag once activated. Bags with minimum (1026 ml) and maximum (2566 ml) fill volumes were dropped from an altitude of 1.8 m, a standard height of IV poles. The chosen test scenario was to resemble bags in use i.e. with open inner seals and mixed content. The number of bags chosen for the earlier drop test (3.2.P.7.3.3 – Mechanical suitability) was according to ISO 15747 and DIN 58363-15 standards. In order to identify weaknesses during production, DIN 58363-15 recommend using 5 containers. Since this test has not been performed earlier, there are no historical data to base the confidence level on. Thereby a

	generous sample size of 10 bags of each size was chosen for the test.
CDRH Review of November 22, 2013 Response	No leaks were observed in the samples evaluated by drop testing, according to the conditions described by the sponsor. The additional information has adequately addressed our deficiency.

CDRH August 16, 2011 Deficiency	<p><i>The Sponsor performed a test to demonstrate that the injection point does not leak when it is punctured by a 23 gauge needle. The test entails puncturing the injection point of the (b) (4) bag with a 23 gauge needle, and then removing the needle. Next, a pressure of 200 mbar (20 kPa) is exerted on the bag for 15 seconds. The bag should demonstrate that it does not leak. From the summary provided in the submission, it appears that the septum at the injection point was punctured only once before subjecting the bag to the 20 kPa pressure. However, from the device description (Section 3.2.P.7.1), it appears that one of the points are 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. The Sponsor should:</i></p> <ol style="list-style-type: none"> <i>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.</i> <i>b. Test the injection point leakage after the septum is punctured with a 19 or 21 gauge needle, as we believe this is more representative of an extreme needle size for penetrating the injection point septum.</i>
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Sponsor June 1, 2012 Response	<p>The injection point of the (b) (4) three chamber bags can be penetrated multiple times and have therefore been tested based on the (b) (4)</p> <p>A description of the test and results are summarized below. Refer to TEST REPORT FOR SELF SEALING TEST included Section 3.2.P.7 for full details on the testing and results.</p>
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	<p>Test description based on (b) (4) "Self-sealing test" Ten bags were tested and a new hypodermic needle with an external diameter of 0.8 mm (21 gauge) is used for each container. Each injection point is pierced 10 times with the needle, each time at a different site. Tightness is tested, by then subjecting the container to an internal overpressure of 270 mbar (27 kPa), for 10 minutes. Atmospheric pressure is then restored and bags left for 30 minutes. Acceptance Criteria: No fluid should escape from the injection point during the test.</p> <p>Result: In total eleven bags were tested from Kabiven batches 10FA2931 (2053 ml), 10FA2930 (2053), 10FA3001 (1540 ml) and 10DFA3002 (1540 ml). All of the bags passed the test based on (b) (4). "Self-sealing test". The port system is the same on all Kabiven bag sizes and bag size has no influence on the result of this test. Therefore the results obtained above are applicable to the entire Kabiven and PeriKabiven product range.</p>
<p>CDRH Review of June 1, 2012 Response</p>	<p>With respect to septum leak resistance, the sponsor describes a test to evaluate the performance of the septum and its resistance to leaking after multiple punctures. Once punctured, the samples are subjected to stress for 10 minutes and then the stress is removed. If after 30 minutes no leaking is observed, the test is considered passing. The state of the samples is not clearly described in the test report. Please describe the following: Please verify that the sample bags were hanging from an IV pole at the highest possible setting. If not, please provide test results using this methodology with all samples selected from the maximum volume bags.</p> <p>The response did not appear to identify any statistically based justification for the use of 10 samples. Please identify the confidence and reliability level (e.g. 95/95) used to select the sample size and describe why that level is acceptable.</p>
<p>Sponsor November 22, 2013 Response</p>	<p>Additional septum leak resistance tests were performed according to the (b) (4) The additive ports of the maximum volume</p>

	<p>bags (2566 ml) were punctured 10 times with a gauge 21G needle and then subjected to an internal pressure of 27 kDa for 10 minutes. Thereafter they were hung vertically for 24 hours before visual inspection.</p> <p>The sample size of 10 bags for the earlier study (3.2.P.7 – Test report for self-sealing test) was chosen based on recommendations in the (b) (4)</p> <p>(b) (4) For the current study, 20 bags were analyzed according to the same acceptance criteria.</p> <p>Acceptance Criteria: No fluid may escape</p> <p>Results: No Leakage observed</p>
<p>CDRH Review of November 22, 2013 Response</p>	<p>The additional data is acceptable and adequately addresses our deficiency.</p>

Biocompatibility Testing

From August 16, 2011 Review

With regard to biocompatibility, the Sponsor has demonstrated that they meet the requirements and recommendations of ISO 10993-4 “Biological evaluation of medical devices – Part 5: Selection of tests for interactions with blood” (hemolysis testing) and ISO 10993-5 “Biological evaluation of medical devices – Part 5: Tests for in-vitro cytotoxicity.” The Sponsor performed an extraction and a toxicological assessment from the extraction studies of the potential migrants from the (b) (4) and the ink used to label the exterior of the bag. Specifically the assessed the following:

- Migration of (b) (4) from the (b) (4) primary bag into lipid emulsions, amino acid solutions and glucose solutions
- Migration of (b) (4) from the (b) (4) primary bag into lipid emulsions, amino acid solutions and glucose solutions
- Migration of (b) (4) from the (b) (4) primary bag into lipid emulsions, amino acid solutions and glucose solutions
- Migration of (b) (4) from the (b) (4) into lipid emulsions, amino acid solutions and glucose solutions
- Migration of (b) (4) into amino acid solutions
- Extraction from the (b) (4) into model solutions
- Extraction of (b) (4) from the (b) (4) into model solutions
- Extraction from (b) (4) into water

Based on these tests, the following conclusions were drawn by the Sponsor:

(b) (4) were evaluated and tested as potential migrants. They were either found in very low concentrations or below their limit of detection.

Small amounts of the process agent (b) (4) were found. In Intralipid 20%, packed in the (b) (4) primary bag, the highest concentrations of (b) (4) was measured to be (b) (4)

that (b) (4) is extracted to the product mainly during (b) (4). A maximum specification limit of (b) (4) µg/g of (b) (4) has been established.

□g/ml after storage at

Based on my assessment of the Sponsor's studies, I do not have any further concern regarding the biocompatibility aspects of the (b) (4) bag.

Human Factors Testing

From August 16, 2011 CDRH review

With regard to Human Factors testing, it appears that the (b) (4) bag is only utilized in a clinical setting by health care providers. Thus, we were going to refrain from questioning whether there are any use-related risks associated in the interaction between the user and device. However, upon receiving a sample of the packaging, FDA found it very cumbersome to manipulate. Thus, to ensure that the use-related risks have been successfully identified and mitigated we recommend the following recommendations with regard to Human Factors Testing:

<p>CDRH August 16, 2011 Deficiency</p>	<p><i>Regarding Human Factors testing, the Sponsor should perform a risk assessment to identify the use-related risks associated with their device, and demonstrate that these risks are no different than the usual risks that clinicians face when delivering drug product through other IV bags, to ensure that there are no unique risks associated with using the (b) (4) bag. Based on this use-related risk assessment, they will have a better idea of the extent to which simulated use testing is required. The Sponsor should review FDA's Guidance Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (July 18, 2000), when developing the appropriate Human Factors studies.</i></p> <p><i>If the Sponsor identifies use-related risk associated with the use of the (b) (4) bag, the Sponsor should conduct Human Factors testing as outlined in CDRH's Guidance (referenced above). A more detailed explanation of the requirements for Human Factors testing is provided in Section 5 "CDRH Recommendation" below.</i></p>
<p>Sponsor June 1, 2012 Response</p>	<p>Human Factors Usability Report – 215091</p>
<p>CDRH Review of June 1, 2012 Response</p>	<p>Please see review from CDRH Human Factors reviewer, LT Quynh Nguyen.</p>

5. CDRH Recommendation

Based on our review, all of the device engineering deficiencies have been adequately resolved.

If you have any questions, please contact CDR Alan Stevens at (301) 796 - 6294.

Digital Signature Concurrence Table	
Reviewer	
Supervisor	

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

/s/

MATTHEW B BRANCAZIO

12/06/2013

Administratively entered into DARRTS for CDRH GHDB reviewer, Alan M Stevens.

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA # 200,656

Name of Drug: Kabiven and [REDACTED] (b) (4)

Applicant: APP Pharmaceuticals, LLC

Labeling Reviewed

Submission Date: January 28, 2011

Receipt Date: January 28, 2011

Label Reviewed: SPL (PDF)

Background and Summary Description

NDA 200656 is being developed [REDACTED] (b) (4)

[REDACTED] (b) (4)

The Agency agreed to a single NDA submission for the 2 dosage strengths based on the User Fees Guidance. This is a 505(b)(2) application where there are multiple reference listed products:

1. Intralipid 20% NDA 18-449 and 20-248
2. Clinimix E sulfite free with electrolytes in dextrose with Calcium NDA 20-678
3. Aminosyn II w/electrolytes in Dextrose with Calcium NDA 19-683
4. Novamine 11.4% Injection NDA 17-957

During a Type B meeting held on July 20, 2009, the Sponsor was asked to address the sodium glycerophosphate component and to justify the electrolyte concentration in their proposed product.

The FDA has approved similar products as 2 chamber bags (Baxter's Clinimix and Clinimix E).

The Sponsor provided rationale for developing the product:

- Avoid manual compounding of admixtures for parenteral nutrition, which in turn decreases the opportunity for microbial contamination, simplifies prescribing, and reduces complicated preparation for both hospital staff and patients
- Reduction of Osmolarity of compounded mixture which permits peripheral administration

Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling format issues are identified on pages 3 through 7 with an “X.”

In addition, the following labeling issues were identified:

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).

Recommendations

All labeling issues identified on pages 3-7 with an “X”, and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by April 26, 2011. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager
Frances Fahnbulleh

Date

Chief, Project Management Staff

Date

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read 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).**”

- **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.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.”
- **Indications and Usage**
 - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
- **Contraindications**
 - This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
 - All contraindications listed in the FPI must also be listed in HL.
 - List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
 - For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.
- **Adverse Reactions**
 - Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
 - For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.
- **Patient Counseling Information Statement**
 - 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”).**”
- **Revision Date**
 - A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

- **Spacing:** white spacing between headings must be consistent

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
 - Align Right column with left column
 - Begin right column with a heading, not a subheading

Full Prescribing Information (FPI)

- **General Format**
 - A horizontal line must separate the TOC and FPI.
 - The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.

- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
 - Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
 - Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
- **Contraindications**
 - For Pregnancy Category X drugs, list pregnancy as a contraindication.
- **Adverse Reactions**
 - 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.
 - For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
 - For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”
- **Use in Specific Populations**
 - Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.
- **Patient Counseling Information**
 - This section is required and cannot be omitted.

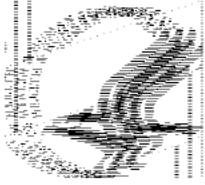
- ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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

/s/

FRANCES G FAHNBULLEH
04/19/2011
RPM Labeling Review

BRIAN K STRONGIN
04/20/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
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Date August 30, 2011

To: Karyn Berry, Medical Officer
Ruyi He, Medical Team Leader

From: Laurie Conklin, MD, Medical Officer
Pediatrics and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Medical Team Leader
Lisa Mathis, MD, Associate Director
Pediatrics and Maternal Health Staff

Regulatory
Project Manager: Mildred Wright

Drug: Kabiven and (b) (4)

Route of
Administration: Intravenous

Sponsor: APP Pharmaceutical

NDA/BLA: # 200-656

Proposed indication:

(b) (4)

(b) (4)

Materials Reviewed: Clinical overview, Midcycle review

Background: Parenteral nutrition (PN) requires the administration of glucose, fat and amino acid solutions. A pharmacist typically formulates these components of PN and adds vitamins, minerals and trace elements. Kabiven and (b) (4) is a single plastic bag divided in to three chambers: fat emulsion, glucose solution and amino acid solution with electrolytes. Intended to be used as a supplement or as the sole source of nutrition provided parenterally, this PN product offers the advantage of a long shelf life (24 months) without need for refrigeration. The benefits of an “all in one” PN product are several, including reduced manipulation of bags and lines minimizing risk of contamination, facilitating delivery and storage for patients on home nutritional, and cost effectiveness for preparation, handling, and delivery. Kabiven and (b) (4) contain Intralipid, which is an approved soybean oil emulsion and is the only currently commercially available lipid source in the US. The Amino Acid solution used in Kabiven and (b) (4) is (b) (4), which the Sponsor asserts (b) (4) the approved product Novamine 11.4%. These amino acid solutions contain all essential and non-essential amino acids except cysteine. However, NDA 17957 for Novamine 11.4% is not marketed in the US and was (b) (4) Novamine 15% appears to be the only strength that has approved labeling in adults, but no pediatric studies are included in labeling.

Regulatory History: Kabiven is not approved for use in the US, but is approved for use in Europe and other countries. Fresenius Kabi is seeking approval by referencing prior findings by the FDA of safety and efficacy for Novamine 11.4% (NDA 017957), dextrose 25% (NDA 019445) and Intralipid 20% (NDA 018449 and 020248). Using sodium glycerophosphate as a precursor for phosphate (b) (4) and possible death that have been associated with inorganic phosphate (FDA safety alert, April 18, 1994). Sodium glycerophosphate is noncompedium in the US, but is compendial in Europe and has a monograph in the European Pharmacopeia. According to the Code of Federal Regulations (21 CFR, Subpart F, Nutrients and/or Dietary Supplements), calcium glycerophosphate, manganese glycerophosphate and potassium glycerophosphate are deemed to be “*Generally Recognized as Safe*”.

Consult Questions from DGIEP:

The sponsor is requesting (b) (4) **Is this** (b) (4) **appropriate** (b) (4)

Currently, TPN products include inorganic phosphate.

Precipitation of calcium and phosphate is the most important physical incompatibility in PN, (b) (4)

(b) (4) Calcium and phosphorus may form an insoluble precipitate that may result in catheter occlusion or microvascular pulmonary emboli. ² On April 18, 1994, the FDA issued a safety alert regarding 3-in-1 TPN solutions, because one institution reported 2 deaths and 2 cases of respiratory distress, which were attributed to a precipitate of calcium phosphate, as autopsies revealed diffuse microvascular pulmonary emboli containing calcium phosphate. The Sponsor states that they have used organic phosphate (sodium glycerophosphate) because (b) (4)

Kabiven and (b) (4) use glycerophosphate (organic phosphate) instead of sodium phosphate (inorganic phosphate). In a recent study, PN solutions were prepared with inorganic and organic calcium and phosphate salts. Calcium phosphate precipitation curves were established by increasing quantities of calcium and phosphate in concentrations ranging from 1 to 50 mmol/L. The most relevant factor in the solubility of calcium phosphate was the nature of the salt, with organic phosphate salt providing the greatest benefit over organic calcium salt in avoiding calcium phosphate precipitation. ¹ A review of the literature reveals no reported concerns regarding the IV administration of organic phosphate and there may be potential benefit.

At a Type B pre-NDA meeting on July 20, 2009, FDA requested additional characterization of sodium glycerophosphate for use in humans. The relative bioavailability between the proposed products and the referenced product was required to be demonstrated by conducting a relative bioavailability study. A Phase 1 study data submitted by the Sponsor included a study to evaluate the relative bioavailability of phosphate from (b) (4) versus glycerophosphate (Glycophos) in healthy adults. Pharmacokinetics appeared to be similar, with similar release of phosphate. Another Phase 1 double-blind, randomized active-controlled study evaluated bioequivalence of phosphate from glycerophosphate vs. sodium phosphates (inorganic phosphate) in healthy adults. Bioequivalence was similar. Notably, according to the Sponsor, the urinary excretion of phosphate from Glycophos was significantly lower compared to inorganic phosphate.

The Sponsor submits that sodium glycerophosphate containing products manufactured by Fresenius Kabi have been administered to approximately (b) (4) people over the last 10 years, with no reported serious adverse events associated with their use. The Sponsor cites in vitro studies in human plasma and rat blood and in vivo PK studies in rats performed by Kabi Pharmacia to evaluate the hydrolysis of the glycerophosphate moiety; specifically the sodium glycerophosphate material is completely hydrolyzed in human plasma into inorganic phosphate.

b) The sponsor is requesting a waiver for use in children < 2 yrs of age, (b) (4)

Is this acceptable?

Commercial amino acid solutions do not contain cysteine, as it converts to its dimeric form and precipitates over time in solution. There is further benefit to the omission of cysteine from Kabiven (per the Sponsor), as this allows for safe (b) (4) of the amino acid solution (b) (4). There are three commercially available FDA-approved amino acid solutions designed for infants (<12 months of age): Aminosyn 10%, TrophAmine 10% and Premasol 10%. None of these solutions contain cysteine and separate preparations of cysteine must be added. These solutions contain taurine, tyrosine, histidine, aspartic acid and glutamic acid, all of which are found in human milk. They contain lower concentrations of methionine, glycine, and phenylalanine than are found in amino acid solutions intended for older patients. The amino acid solutions designed for individuals ≥ 1 year of age, containing different combinations of essential and nonessential amino acids, are as follows: Aminosyn 3.5%, Aminosyn II 3.5%, FreAmine III 10%, Novamine 15%, and Travasol 10%.⁹

PMHS Recommendations:

1. The use of glycerophosphate, an organic phosphate, is supported by in vitro and in vivo studies conducted by the Sponsor. It is also supported by BE and PK studies done in adults. There is wide use of this product outside of the US safely, by report. However, there is no approved product containing sodium glycerophosphate in the US. It is considered a new active ingredient and these multichamber bags are considered a new combination

PMHS communicated these recommendations to DGEIP during a meeting on August 15, 2011 and has provided input [REDACTED] (b) (4).

After these meetings, the CMC reviewers identified a potential issue regarding the heavy metal content of Kabiven solutions, focusing on lead, mercury, cadmium, and arsenic. Additional heavy metals (such as aluminum) may also be of interest in the pediatric population.

1. Bouchoud L, Fonzo-Christe C, Sadeghipour F, et al. Maximizing calcium and phosphate content in neonatal parenteral nutrition solutions using organic calcium and phosphate salts. *Journal of Parenteral and Enteral Nutrition* 2010; 34: 542-45.
2. Reedy JS, Kuhlman JE, Voytovich M. Microvascular pulmonary emboli secondary to precipitated crystals in a patient receiving total parenteral nutrition: a case report and description of the high-resolution CT findings. *Chest* 1999; 115: 892-5.
3. Sturman JA, Gaull G, Raiha NC. Absence of cystathionase in human fetal liver: is cystine essential? *Science* 1970; 169: 74-76
4. Pascal TA, Gillam BM, Gaull GE. Cystathionase: immunochemical evidence for absence from human fetal liver. *Pediatr Res* 1972; 6: 773-8.
5. Gaull G, Sturman JA, Raiha NC. Development of mammalian sulfur metabolism: absence of cystathionase in human fetal tissues. *Pediatr Res* 1972; 6: 538-47.
6. Pohlandt F. Cystine: a semi-essential amino acid in the newborn infant. *Acta Paediatr Scand* 1974; 63: 801-4.
7. Kanaya S, Nose I, Harada T, et al. Total parenteral nutrition with a new amino acid solution for infants. *J Pediatr Gastroenterol Nutr* 1984; 3: 440-5.
8. Courtney-Martin G, Moore AM, Ball RO, et al. The addition of cysteine to the total sulphur amino acid requirement as methionine does not increase erythrocytes glutathione synthesis in the parenterally fed human neonate. *Pediatric Research* 2010; 67: 320-4.
9. American Academy of Pediatrics *Pediatric Nutrition Handbook*, 6th Edition. Ronald Kleinman, ed. Elk Grove Village IL: 2009. Appendix T-1, p 1363.
10. American Academy of Pediatrics *Pediatric Nutrition Handbook*, 6th Edition. Ronald Kleinman, ed. Elk Grove Village IL: 2009. Table 22.2, p.523

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

/s/

LAURIE S CONKLIN
08/30/2011

HARI C SACHS
08/30/2011
I agree with the recommendations in this consult.

LISA L MATHIS
09/06/2011

MEMORANDUM

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

DATE: August 17, 2011

TO: DGIEP/HFD-180

THROUGH: N/A

FROM: CDRH

SUBJECT: CDRH Consult Review for new NDA Application

APPLICATION/DRUG: NDA 200-656, Kabiven and (b) (4) (lipid injectable emulsion with amino acids and electrolytes and dextrose)

The sponsor (APP Pharmaceuticals) submitted NDA application 200-656 on January 28, 2011. NDA 200-656 (Kabiven and (b) (4)) is a 505(b)(2) application whose proposed indication is to provide patients in need of total parenteral nutrition with appropriate amounts of amino acids, glucose, (b) (4), electrolytes and (b) (4) in plastic bags, subdivided into 3 chambers. One chamber contains lipids, a second chamber contains amino acids with electrolytes, and a third chamber contains dextrose. Peelable seals separate the chambers, so the container is easily activated. An additive port provides flexibility to include vitamins and other ingredients for TPN. The CMC review team requested that CDRH evaluate the mechanism by which the compartments are kept separated until time to administer the admixture.

The PDUFA goal date for this application is November 28, 2011. CDRH has completed the consult review. The attached documents contain comments and recommendations to be conveyed to the sponsor.

Please see the attached documents:

- 1) DGP consult request to CDRH (dated July 13, 2011)
- 2) CDRH consult review from Nikhil Thakur, Senior Engineering Reviewer (dated August 16, 2011)

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: 8/16/2011

Reviewer Initials: NT

Supervisory Concurrence: JM

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH/DAGID

Division: GHDB

Mail Code: HF D 470

Consulting Reviewer Name: Nikhil Thankur

Building/Room #: WO 66 Rm 2562

Phone #: 301-796-5536

Fax #:

Email Address: nikhil.thankur@fda.hhs.gov

RPM/CSO Name and Mail Code:

Cheryl Mackey 301-796-6651

From (Originating Center):

Center: CDER

Division: DGEP

Mail Code: HFD 180

Requesting Reviewer Name: Marie Kowblansky/ Terun Mehta

Building/Room #: WO 22/ 1454

Phone#: 301-796-1390

Fax #:

Email Address: marie.kowblansky@fda.hhs.gov

RPM/CSO Name and Mail Code: Frances Fahnbulleh, HFD 180

Requesting Reviewer's Concurring

Supervisor's Name: Moo Jong Rhee

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: June 7, 2011

Requested Completion Date: July 13, 2011

Submission/Application Number: 200-656
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: JANUARY 28, 2011

Official Submission Due Date: November 28, 2011

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

Name of Firm: APP Pharmaceuticals, LLC

Intended Use: NDA 200-656 (Kabiven and (b) (4)) is a 505(b)(2) which has been developed to provide patients in need of total parenteral nutrition with appropriate amounts of amino acids, glucose, (b) (4) electrolytes and (b) (4) in plastic bags, subdivided into 3 chambers.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

The following links to this NDA submission are being provided:
EDR Location: \\CDSESUB1\EVSPROD\NDA200656\200656.enx
Cover Letter: \\CDSESUB1\EVSPROD\NDA200656\0000\m1\us\cover-letter-nda-200656.pdf
Letter Date: 01/28/2011
Stamp Date: 1/28/2011

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

The TPN concept assumes that all requirements for macronutrients (electrolytes, vitamins, and trace elements) are met through the parenteral administration of an "all-in-one" (AIO) sterile admixture or product. Kabiven and (b) (4) are two such products that supply nutritional therapy by providing sterile, (b) (4) solutions using innovative 3-chamber bag (3CB) technology. One chamber contains lipids, a second chamber contains amino acids with electrolytes, and a third chamber contains dextrose. Peel seals separate the chambers, so the container is easily activated. An additive port provides flexibility to include vitamins and other ingredients for TPN. We request that you evaluate the mechanism by which the compartments are kept separated until time to administer the admixture.



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: August 16, 2011

From: Nikhil Thakur, LCDR USPHS, Senior Engineering Reviewer, WO66, RM 2562
CDRH/ODE/DAGID/General Hospital Devices Branch (GHDB)

To: Frances Fahnbulleh, Ph. D, Chemist, WO 22, Room 5215
CDER/OND/ODE3/DGIEP

Subject: CDRH Consult, NDA 200656, (b) (4), APP Pharmaceuticals
(Multi-Chamber IV Bag to store, mix and dispense Kabiven and (b) (4))

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 200656. The device constituent of this combination product consists of a Multi Chamber Plastic IV Bag for the delivery of Kabiven and (b) (4).

2. Device Description

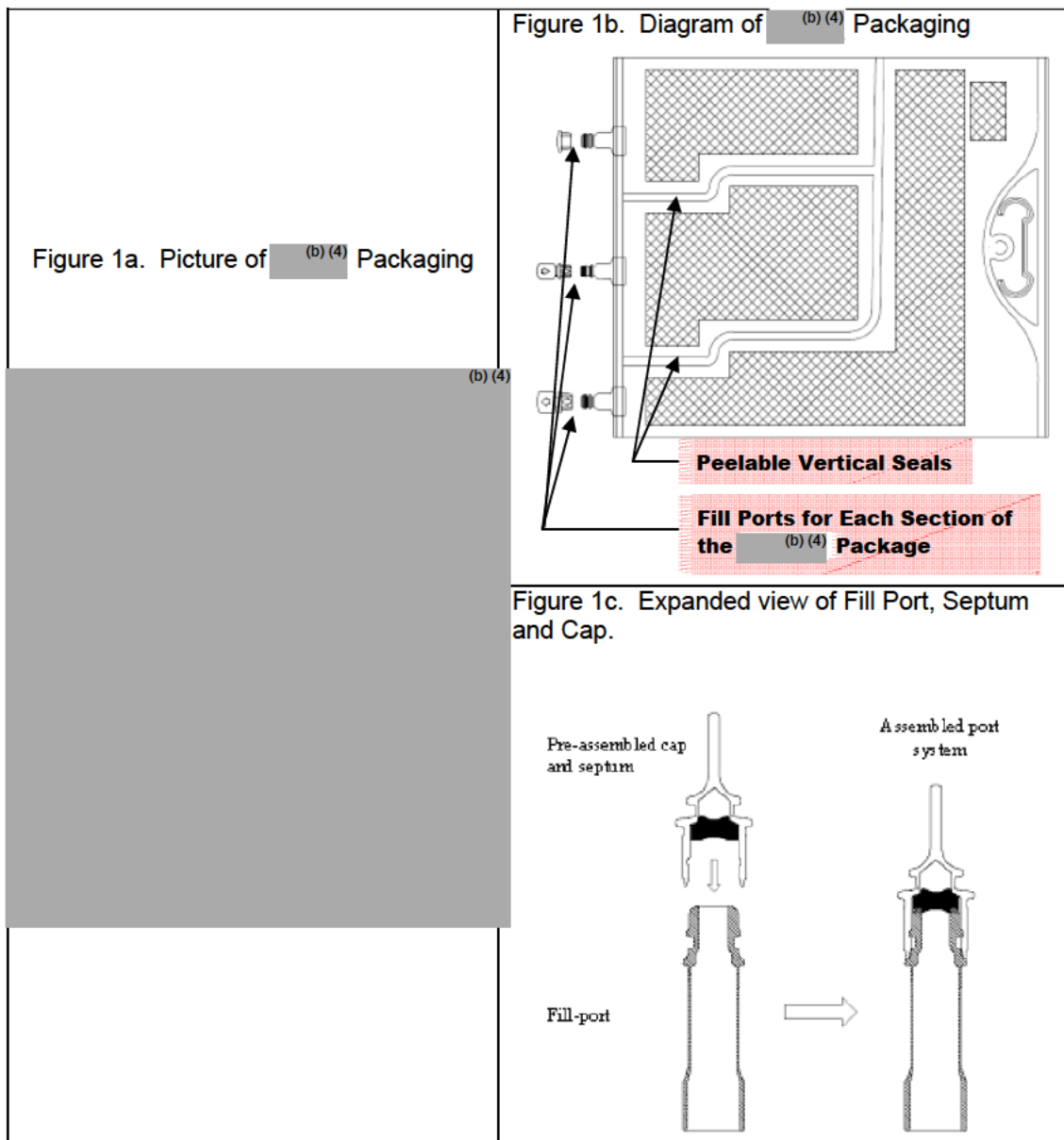
The Kabiven and (b) (4) is packaged in a flexible three chamber bag called the (b) (4) packaging system. This system has been developed by the company, Fresenius Kabi. The packaging system is depicted in Figure 1a below.

The primary bag is produced from (b) (4)

(b) (4)

The cap is not in direct contact with the infusion solutions. One of the ports is used for making injections to the bag after mixing, another port is used for infusion through an infusion set with an infusion spike and the third port is a blind port, used only for filling the bag.

Figure 1. Picture and Diagram of (b) (4) Packaging



3. Documents Reviewed

NDA 200656 – Original Submission (Dated January 28, 2011) and Subsequent Amendments
Amendment 1 – Dated March 10, 2011
Amendment 2 – Dated April 6, 2011
Amendment 3 – Dated April 25, 2011
Amendment 4 – Dated May 10, 2011
Amendment 5 – Dated June 17, 2011
Amendment 6 – Dated July 7, 2011
Amendment 7 – Dated July 27, 2011
Amendment 8 – Dated July 27, 2011
Amendment 9 – Dated August 5, 2011
ISO 15747 “Plastic containers for intravenous injection”

D IN 58363 "Infusion containers and accessories." Part 15 "Infusion bags and bottles made of plastic. Requirements and testing."

4. CDRH Review and Comments

CDRH's Review of the device constituent for this Combination Product consisted of an assessment of Device Performance, Human Factors, and Biocompatibility.

CDRH did not review (b) (4) because this aspect of the device is being reviewed by CDER. This device does not contain Electrical and/or Software Components.

General

The (b) (4) packaging bag would typically be considered to be a primary container / closure for the Kabiven and (b) (4) drug product, if it were a single chamber IV bag. However, given that there are multiple chambers, and multiple steps that the user must take to manipulate the bag in order to prepare the drug product (i.e. remove the seals separating each chamber, mix the contents to achieve a homogeneous solution, etc.). As a result, CDRH is providing this consult to express our questions and concerns regarding the (b) (4) packaging.

Functional / Mechanical Testing

In the original submission, Section 3.2.P.7.3, Subsection 4 contained a summary of the physical testing on the (b) (4) packaging. The Sponsor stated that they followed the testing recommendation within ISO 15747 "Plastic containers for intravenous injection" and D IN 58363 "Infusion containers and accessories." Part 15 "Infusion bags and bottles made of plastic. Requirements and testing." However, these standards have not been reviewed by CDRH, and thus the Center has not recognized them. Thus, CDRH is unclear whether they adequately address the concerns regarding the safety and effectiveness of the (b) (4) packaging. We have the following concerns:

1. The Sponsor performed a test to demonstrate the (b) (4) packaging's resistance to temperature, pressure and leakage, per the recommendations within ISO 15747 and D IN 58363-15. Based on the description of the test within these standards, it is unclear whether altitude was accounted for as part of testing regimen. For instance, the Sponsor's test states that the (b) (4) bag is conditioned for 24 hours at a temperature of 50 +/- 5 Deg. C. The bag is then exposed to a pressure of 500 mbar (50 kPa) for 15 seconds. The bag is considered to pass the test if it does not leak any fluids. Our concern is that atmospheric pressure changes significantly with altitude (for example, the typical atmospheric pressure in Denver, Colorado, which is approximately 1 mile above sea level, is approximately 85 kPa). Given the difference in pressure based on varying altitude, temperature and humidity, we believe that it is more relevant to demonstrate the pressure at which the (b) (4) bag bursts. If the burst pressure significantly exceeds (factor of 2x) the typical change in atmospheric pressure as it relates to altitude, then our concerns of the bag bursting due to this environmental change will have been mitigated. The Sponsor should utilize a statistically significant sample size when performing this test. The Sponsor should use basic statistical analyses when interpreting the test results.

2.

(b) (4)

3. The Sponsor performed a test to demonstrate that the injection point does not leak when it is punctured by a 23 gauge needle. The test entails puncturing the injection point of the (b) (4) bag with a 23 gauge needle, and then removing the needle. Next, a pressure of 200 mbar (20 kPa) is exerted on the bag for 15 seconds. The bag should demonstrate that it does not leak. From the summary provided in the submission, it appears that the septum at the injection point was punctured only once before subjecting the bag to the 20 kPa pressure. However, from the device description (Section 3.2.P.7.1), it appears that one of the points are 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. The Sponsor should:
- 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.
 - Test the injection point leakage after the septum is punctured with a 19 or 21 gauge needle, as we believe this is more representative of an extreme needle size for penetrating the injection point septum.

Biocompatibility Testing

With regard to biocompatibility, the Sponsor has demonstrated that they meet the requirements and recommendations of ISO 10993-4 "Biological evaluation of medical devices – Part 5: Selection of tests for interactions with blood" (hemolysis testing) and ISO 10993-5 "Biological evaluation of medical devices – Part 5: Tests for in-vitro cytotoxicity." The Sponsor performed an extraction and a toxicological assessment from the extraction studies of the potential migrants from the (b) (4) and the ink used to label the exterior of the bag. Specifically the assessed the following:

- Migration of (b) (4) from the (b) (4) primary bag into lipid emulsions, amino acid solutions and glucose solutions
- Migration of (b) (4) from the (b) (4) primary bag into lipid emulsions, amino acid solutions and glucose solutions
- Migration of (b) (4) from the (b) (4) primary bag into lipid emulsions, amino acid solutions and glucose solutions
- Migration of (b) (4) from the (b) (4) into lipid emulsions, amino acid solutions and glucose solutions
- Migration of (b) (4) into amino acid solutions
- Extraction from the (b) (4) into model solutions
- Extraction of (b) (4) from the (b) (4) into model solutions
- Extraction from (b) (4) into water

Based on these tests, the following conclusions were drawn by the Sponsor:

(b) (4) were evaluated and tested as potential migrants. They were either found in very low concentrations or below their limit of detection.

Small amounts of the process agent (b) (4) were found. In Intralipid 20%, packed in the (b) (4) primary bag, the highest concentrations of (b) (4) was measured to be (b) (4) □g/ml after storage at accelerated conditions (40 °C/25% RH). It has been concluded

that (b) (4) is extracted to the product mainly during (b) (4). A maximum specification limit of (b) (4) µg/g of (b) (4) has been established.

Based on my assessment of the Sponsor's studies, I do not have any further concern regarding the biocompatibility aspects of the (b) (4) bag.

Human Factors Testing

With regard to Human Factors testing, it appears that the (b) (4) bag is only utilized in a clinical setting by health care providers. Thus, we were going to refrain from questioning whether there are any use-related risks associated in the interaction between the user and device. However, upon receiving a sample of the packaging, FDA found it very cumbersome to manipulate. Thus, to ensure that the use-related risks have been successfully identified and mitigated we recommend the following recommendations with regard to Human Factors Testing:

4. Regarding Human Factors testing, the Sponsor should perform a risk assessment to identify the use-related risks associated with their device, and demonstrate that these risks are no different than the usual risks that clinicians face when delivering drug product through other IV bags, to ensure that there are no unique risks associated with using the (b) (4) bag. Based on this use-related risk assessment, they will have a better idea of the extent to which simulated use testing is required. The Sponsor should review FDA's Guidance Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (July 18, 2000), when developing the appropriate Human Factors studies.

If the Sponsor identifies use-related risk associated with the use of the (b) (4) bag, the Sponsor should conduct Human Factors testing as outlined in CDRH's Guidance (referenced above). A more detailed explanation of the requirements for Human Factors testing is provided in Section 5 "CDRH Recommendation" below.

5. CDRH Recommendation

Based on our review, the following questions and concerns should be conveyed to the Sponsor:

Device Performance

1. You performed a test to demonstrate the (b) (4) packaging's resistance to temperature, pressure and leakage, per the recommendations within ISO 15747 and D IN 58363-15. Based on the description of the test within these standards, it is unclear whether altitude was accounted for as part of testing regimen. For instance, your test states that the (b) (4) bag is conditioned for 24 hours at a temperature of 50 +/- 5 Deg. C. The bag is then exposed to a pressure of 500 mbar (50 kPa) for 15 seconds. The bag is considered to pass the test if it does not leak any fluids. Our concern is that atmospheric pressure changes significantly with altitude (for example, the typical atmospheric pressure in Denver, Colorado, which is approximately 1 mile above sea level, is approximately 85 kPa). Given the difference in pressure based on varying altitude, temperature and humidity, we believe that it is more relevant to demonstrate the pressure at which the (b) (4) bag bursts. If the burst pressure significantly exceeds (factor of 2x) the typical change in atmospheric pressure as it relates to altitude, then our concerns of the bag bursting due to this environmental change will have been mitigated. You should utilize a statistically significant sample size when performing this test. You should use basic statistical analyses when interpreting the test results.

2. (b) (4)

3. You performed a test to demonstrate that the injection point does not leak when it is punctured by a 23 gauge needle. The test entails puncturing the injection point of the (b) (4) bag with a 23 gauge needle, and then removing the needle. Next, a pressure of 200 mbar (20 kPa) is exerted on the bag for 15 seconds. The bag should demonstrate that it does not leak. From the summary provided in the submission, it appears that the septum at the injection point was punctured only once before subjecting the bag to the 20 kPa pressure. However, from the device description (Section 3.2.P.7.1), it appears that one of the points are 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. You should:
- 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.
 - Test the injection point leakage after the septum is punctured with a 19 or 21 gauge needle, as we believe this is more representative of an extreme needle size for penetrating the injection point septum.

Human Factors

4. Regarding Human Factors testing, you should perform a risk assessment to identify the use-related risks associated with their device, and demonstrate that these risks are no different than the usual risks that clinicians face when delivering drug product through other IV bags, to ensure that there are no unique risks associated with using the (b) (4) bag. Based on this use-related risk assessment, you will have a better idea of the extent to which simulated use testing is required. You should review FDA's Guidance Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (July 18, 2000), when developing the appropriate Human Factors studies.

If you identify use-related risk associated with the use of the (b) (4) bag, you should conduct Human Factors testing as outlined in CDRH's Guidance (referenced above). When performing this testing, you should consider the following:

a. Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials.

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, the Agency expects that the results

demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

b. User Tasks and Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. 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.

Please provide a use-related risk analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

c. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

d. Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels, level of disabilities/impairments) will use your device, you should include 15 from each distinct group.

For devices that are intended to be marketed within the United States (US), we expect that the human factors testing would be conducted in the US with (American) English speaking participants.

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

e. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test 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 facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, 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. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

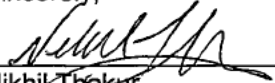
Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something 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.

Please describe and provide a rationale for including each type of data you collect.

- f. Protocol
CDRH has offered to review Human Factors Protocols to ensure that the protocol is aligned with the rationale expressed in the Human Factors Guidance document. If you would like your protocol to be reviewed, prior to conducting the Human Factors study, please provide a proposed protocol for the Agency to review through the appropriate Office / Division within CDER. CDER will forward the protocol to CDRH for assessment.

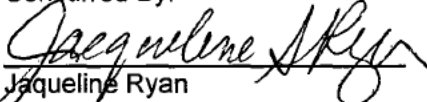
If you have any questions, please contact Nikhil Thakur at (301) 796 - 5536.

Sincerely,



Nikhil Thakur
Senior Engineering Reviewer

Concurred By:



Jacqueline Ryan
Combination Product Team Leader

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

/s/

FRANCES G FAHNBULLEH
09/02/2011
CDRH Consult Review

MEMORANDUM

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

DATE: August 14, 2011

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology Products (DGP)
Office of Drug Evaluation III

Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology 3
(DCP3)

FROM: Xikui Chen, Ph.D., Chemist
Division of Bioequivalence and GLP Compliance
(DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT:

TM

(b) (4)

Sponsored by APP Pharmaceuticals, LLC

At the request of the Division of Gastroenterology Products (DGP), and the Division of Clinical Pharmacology 3, DBGC audited the clinical and analytical portions of the following study:

Study Number: Glyc-001-C P1

Study Title: "Single-Centre, Double-Blind, Randomized, Two-Treatment, Two-Sequence, Active-Controlled

Phase-I-Study to Evaluate Bioequivalence of Phosphate from Glycerophosphate (Glycophos®) versus Sodium Phosphates (Hospira, Inc, USA) in Healthy Subjects”

The clinical portion of Study Glyc-001-C P1 was conducted at PAREXEL International GmbH, Early Phase Clinical Unit - Berlin, Haus 18, Spandauer Damm 130, 14050 Berlin, Germany. Following inspection of the clinical site (July 28, and August 1 to 5, 2011), no Form FDA-483 was issued.

Audit of the

S
(b) (4)

(b) (4) Following inspection at the analytical site (b) (4), For (b) (4) 3 was issued (Attachment 1). DBGC received the (b) (4) written response through email to the inspection finding on (b) (4), 2011 (Attachment 2). The FDA-483 observation, (b) (4) written response, and our evaluation are as follows:

1. Failure to include sufficient calibrator and quality control samples in each analytical run.

Specifically, only one calibrator at 1.67 mmol/L phosphate and deionized water were used for a calibration curve. Only two quality control samples (QCs) at approximately 1.3 and 2.1 mmol/L phosphate were used for serum samples, and two QCs at 8.3 and 16.1 mmol/L phosphorus were used for urine samples.

During the inspection, we observed that one calibrator at 1.67 mmol/L phosphate was utilized to calibrate the Cobas 1 instrument on July 14, 2010, and November 4, 2010, and Cobas 2 on August 19, 2010, and November 3, 2010, respectively. The study serum samples were analyzed from September 7 to 29, 2010, and urine samples were analyzed from September 1 to 28, 2010, on Cobas 1 or Cobas 2. By using one calibrator and deionized water, the measuring range on Cobas is 0.10-6.46 mmol/L phosphate in serum and 1.1-92 mmol/L phosphate in urine samples according to the Cobas PHOS2 insert. The calibrator was not used during the period of analyses of study samples. Two quality control samples (QCs) at approximately 1.3 mmol/L phosphate in Precinorm U (PNU) and 2.1 mmol/L phosphate in Precipath U (PPU) were used for serum samples, and two QCs at 8.3

mmol/L phosphorus in Liquichek Urine Control 1 and 16.1 mmol/L phosphorus in Liquichek Urine Control 2 were used for urine samples. The two quality controls (1.3 and 2.1 mmol/L) employed in the serum samples during the study did not meet the recommendations in FDA guidance for three concentrations in the range of study samples to demonstrate the accuracy of a method. The maximum observed phosphate concentrations for serum samples were 3.38 mmol/L after the test product, and 4.20 mmol/L after the reference, respectively. The two quality controls (8.3 and 16.3 mmol/L) utilized in the urine samples during the study were not representative of study urine sample concentrations, since approximately 164 urine samples were re-analyzed due to their concentration above the measuring upper limit 92 mmol/L.

In the response from (b) (4) the firm provided calibration standards in the appendix 6 and 7. The firm also provided 2 external quality assurances for serum samples and 2 external quality assurances for urine samples in appendix 10, and stated that external quality assurance samples cover the study samples.

Concentration of the four external quality assurances could not be located in the appendix 10. However, the concentrations of external quality assurances listed in the analytical report (study No.: Glyc-001-C P1) ranged 0.959 to 2.48 mmol/L in serum and 4.61 to 18.8 mmol/L in urine. The concentrations in external quality assurances were the same as used in internal quality controls. The quality control samples were not representative of the study samples, and the analytical method was insufficiently demonstrated to be accurate during the study.

Conclusion:

Following the above inspections, DBGC recommends that the phosphate data from study **Glyc-001-C P1** should **not** be accepted for Agency review, because the quality control samples did not represent the study samples, and the analytical method was insufficiently demonstrated to be accurate during the study for the purposes of this bioequivalence assessment.

TM

(b) (4)

and

(b) (4)

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Xikui Chen, Ph.D.

Final Classification:

Clinical

PAREXEL International GmbH, Early Phase Clinical Unit -
Berlin, Haus 18, Spandauer Damm 130, 14050 Berlin, Germany
- NAI

Analytical

(b) (4)

(b) (4)

cc: DARRTS
OSI/Ball
DBGC/Salewski/Haidar//Yau/Viswanathan/Skelly/Chen/Djernett/
Mathews/CF
OND/DGP/Donna Griebel/Frances Fahnbulleh
OTS/OCP/DCPIII/Dennis Bashaw
HFR-CE350/Jonee Mearns

Draft: XC 8/12/11
Edit: MFS 8/12/11

DSI: File BE6200; O:\BE\EIRCover\200656app.pho.doc
FACTS 1283377

cc: email
CDER DSI PM TRACK

183 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

XIKUI CHEN
08/14/2011

MICHAEL F SKELLY
08/15/2011
Skelly signing on behalf of Dr. Martin Yau

SAM H HAIDAR
08/15/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 200,656	NDA Supplement #:S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Kabiven™ (b) (4) and (b) (4) (Sponsor to send in request for name review)		
Established/Proper Name: Same as above (CMC to further consider correct name)		
Dosage Form: (b) (4)		
Strengths: (b) (4)		
Applicant: APP Pharmaceuticals, LLC (Fresenius Kabi-Manufacturer)		
Agent for Applicant (if applicable): N/A		
Date of Application: January 28, 2011 Date of Receipt: January 28, 2011 Date clock started after UN: N/A		
PDUFA Goal Date: November 28, 2011	Action Goal Date (if different): November 28, 2011	
Filing Date: March 29, 2011	Date of Filing Meeting: March 23, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : Type 4 application –New Combination of Active Ingredients		
Proposed indication(s): Total Parenteral (b) (4)		
<div style="background-color: #cccccc; height: 100px; width: 100%;"></div>		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
<input type="checkbox"/> Tropical Disease Priority Review Voucher submitted		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system	

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

- Pre-filled biologic delivery device/system
- Device coated/impregnated/combined with drug
- Device coated/impregnated/combined with biologic
- Drug/Biologic
- Separate products requiring cross-labeling
- Possible combination based on cross-labeling of separate products
- Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): 105,282				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				N/A
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>			X	
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				N/A

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			Under M 1.2
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			Under 1.3.3

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				N/A- Field Office has access to Certification in EDR

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>				N/A

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			New active ingredient (sodium glycerophosphate)
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			Sponsor requested (b) (4)
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Sponsor was asked to submit a name request for review to DMEPA
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				N/A
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Label will be forwarded to DDMAC as part of the NDA review
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			CDRH-OCP for 3 chamber system
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 20, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			Placed in eroom
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 29, 2011

BLA/NDA/Supp #: 200-656

PROPRIETARY NAME: Kabiven (b) (4)

ESTABLISHED/PROPER NAME: Same as above

DOSAGE FORM/STRENGTH:

Intravenous (b) (4) into a central or peripheral vein (after mixing)
(b) (4) and (b) (4)

APPLICANT: APP Pharmaceuticals, LLC

PROPOSED INDICATION(S):

(b) (4)

(b) (4)

BACKGROUND: The Agency agreed to a single NDA submission for the 2 dosage strengths based on the User Fees Guidance. This is a 505(b)(2) application where there are multiple reference listed products:

1. Intralipid 20% NDA 18-449 and 20-248
2. Clinimix E sulfite free with electrolytes in dextrose with Calcium NDA 20-678
3. Aminosyn II w/electrolytes in Dextrose with Calcium NDA 19-683
4. Novamine 11.4% Injection NDA 17-957

During a Type B meeting held on July 20, 2009, the Sponsor was asked to address the sodium glycerophosphate component and to justify the electrolyte concentration in their proposed product. The FDA has approved similar products as 2 chamber bags (Baxter's Clinimix and Clinimix E).

The Sponsor provides rationale for developing the product:

- Avoid manual compounding of admixtures for parenteral nutrition, which in turn decreases the opportunity for microbial contamination, simplifies prescribing, and reduces complicated preparation for both hospital staff and patients

- Reduction of Osmolarity of compounded mixture which permits peripheral administration ((b) (4))

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Frances Fahnbulleh	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Ruyi He		Y
Clinical	Reviewer:	Karyn Berry	Y
	TL:	Ruyi He	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Sandhya Apparaju	Y
	TL:	Sue Chih Lee	Y
Biostatistics (NAI)	Reviewer:	Behrang Vali	Y
	TL:	Mike Welch	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Babatunde Akinshola	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Tarun Mehta	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Denise Miller	Y
	TL:	James L. McVey	N
CMC Labeling Review	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:	Francis Goodwin (DMPQ)	N
	TL:	Francis Goodwin (Acting TL)	N
OSE/DMEPA (proprietary name)	Reviewer:	Nitin Patel (RPM)	Y
	TL:	Doris Bates	N
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Joyce Korvick, M.D. (Deputy Director for Safety)		Y
	Donna Griebel, M.D. (Director-DGIEP)		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: No pivotal clinical trials were done</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <i>this drug is not the first in its class</i>

<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: NAI</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, MD, Director, OND, ODE III	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Filing Goal Date: 3/29/11 74-Day Letter due: 4/12/11 PDUFA Date: 11/28/11	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). N/A
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. N/A
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	<p>If priority review: N/A</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action N/A [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

FRANCES G FAHNBULLEH

04/19/2011

RPM Filing Review

BRIAN K STRONGIN

04/20/2011