

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200656Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: August 21, 2014

TO: **Addendum to Review #2** of NDA 200656, dated June 11, 2014

FROM: Tarun Mehta, M.Sc.
Review Chemist, ONDQA

THROUGH: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV, ONDQA

SUBJECT: **Finalized Labels/Labeling**

The previous addendum (6/11/14) for the final APPROVAL recommendation addressed unresolved labeling issues noted in the Review #2 (5/22/14). However, further changes have been made in the labels during the labeling review including SEALD team, and final revised labels were submitted on 8/21/14 (see **Attachments**), which are deemed satisfactory.

- Established name is changed to “Amino acids, electrolytes, dextrose, and lipid injectable emulsion” for intravenous use.
- Strengths were presented in line with the active ingredients.
- Rephrasing of “(b) (4)” to “(b) (4)” wording in the product name and in the description section of PI

Comment/Recommendation

The changes made in the labels are satisfactory, and the previous APPROVAL recommendation made in the Addendum made on June 11, 2014, is still valid.

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

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/s/

TARUN D MEHTA
08/21/2014

MOO JHONG RHEE
08/22/2014
Chief, Branch IV

MEMORANDUM

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

DATE: June 10, 2014

TO: Review #2 of NDA 200656, dated May 22, 2014

FROM: Tarun Mehta, M.Sc.
Review Chemist, ONDQA

THROUGH: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV, ONDQA

SUBJECT: **Final Approval Recommendation.**

The CMC Review #2 noted the following labeling issues:

1. Font size of the established name should be enlarged.
2. Lot number and expiration dating period are missing.
3. Regarding PI Labeling:
Storage temperature in How Supplied section should follow the USP format.

Because of these unresolved issues, this NDA was not deemed ready for approval from ONDQA perspective.

On May 27, 2014, additional stability data up to 24 months was submitted in the amendment 0033 with satisfactory results including no particulates observed in the product bags.

On May 30, 2014, the applicant has revised the labels of immediate container closures of Kabiven and Perikabiven with “batch number”, “manufacture date”, and “(b) (4)”. Also the storage temperature was revised in accordance with the USP format.

On June 6, 2014, the font size of the established name was increased to the extent of at least 50% via the amendment 0036 for all (Kebivan 1026mL, 1540mL, 2053mL, 2566mL and Perikabiven 1440mL, 1920mL and 2400L) packaging size. (See the **Attachments I and II**)

Recommendation:

Based on the revised labels for the immediate container/closures as well as conformance of the storage temperature in the “How Supplied” section of PI to the USP format, this NDA is now recommended for **APPROVAL** from the ONDQA perspective with an **expiration dating period of 24 months.**

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/s/

TARUN D MEHTA
06/11/2014

MOO JHONG RHEE
06/11/2014
Chief, Branch IV

NDA 200656

Kabiven™

Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose

(b) (4)

AND

PeriKabiven™

Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose

(b) (4)

APP Pharmaceuticals.

(a company of the Fresenius Kabi Group)

Tarun Mehta

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

CMC REVIEW OF NDA 200656
For the Division of Gastroenterology Products (HFD-180)

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 200656
2. REVIEW #: 2
3. REVIEW DATE: 22-May-2014
4. REVIEWER: Tarun Mehta
5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	January/31/ 2011
Amendment 0001	March/10/ 2011
Amendment 0002	April/06/2011
Amendment 0003	April/25/2011
Amendment 0004	May/10/2011
Amendment 0007	July/27/2011
Amendment 0011	September/7/2011
Amendment 0012	September/16/2011
Amendment 0015	November/14/2011

6. SUBMISSION(S) BEING REVIEWED:

Amendment 0016	November/18/2011
Resubmission (0017)	June /1 / 2012
Resubmission	November/ 25/2013
Amendment 0018 (CDRH only)	August /24/2012
Amendment 0020 (DMEPA)	November/19/2012
Amendment 0025 (CR response)	November/25/2013
Amendment 0026 (Elemental impurity method validation)	January/ 13/ 2014
Amendment 0028	February/03/2014

CMC Review Data Sheet

Amendment 0029 (Toxicology)	February/20/2014
Amendment 0030 (Usability)	March / 25/ 2014
Amendment 0031	April / 29 /2014

7. NAME & ADDRESS OF APPLICANT:

Name: APP Pharmaceutical, LLC (a company of the Fresenius Kabi Group)
Address: 1501 East Woodfield Road, Suite 300E
Schaumburg, IL 60173
Representative: Aparna Dagar, Ph.D.
Telephone: (847) 969-2706

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kabiven™ and PeriKabiven™
- b) Non-Proprietary Name: Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose
- c) Code Name/# (ONDQA only): None
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 2
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Total parenteral nutrition

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: (b)(4) kcal/L and (b)(4) kcal/L

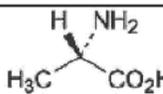
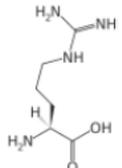
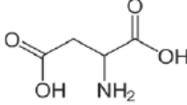
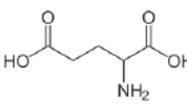
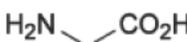
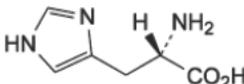
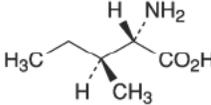
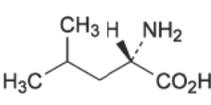
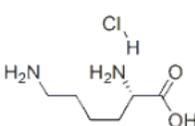
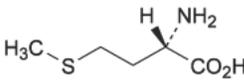
13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

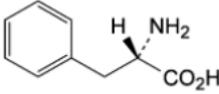
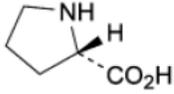
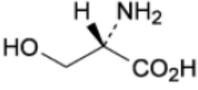
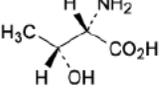
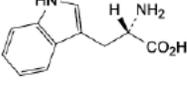
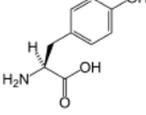
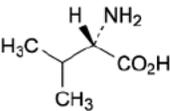
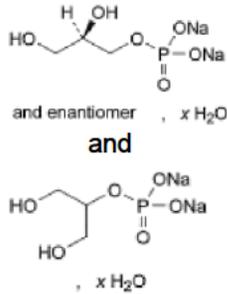
CMC Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

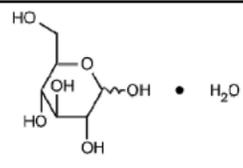
Chemical names, compendial names, structural formulas, abbreviations for active ingredients:

Chemical Name	INN name	Abbreviation	structural formula	MW g/mol	MF
(S)-2-Aminopropanoic acid CAS # 56-41-7	L- Alanine	L-ALA		89.1	C ₃ H ₇ NO ₂
(S)-2-amino-5-guanidinopentanoic acid CAS# 74-79-3	L-Arginine	L-ARF		174.20	C ₆ H ₁₄ N ₄ O ₂
(2S)-2-aminobutanedioic acid CAS# 56-84-8	L- Aspartic Acid	L- ASP		133.10	C ₄ H ₇ NO ₄
(2S)-2-aminopentanedioic acid CAS# 56-86-0	L-Glutamic Acid	L - GA		147.1	C ₅ H ₉ NO ₄
2-Aminoacetic acid CAS# 56-40-6	Glycine	Gly		75.1	C ₂ H ₅ NO ₂
(S)-2-Amino-3-(imidazol-4-yl)propanoic acid CAS# 71-00-1	L- Histidine	L-HISF		155.2	C ₆ H ₉ N ₃ O ₂
(2S,3S)-2-Amino-3-methylpentanoic acid CAS# 73-32-5	L - Isoleucine	L - ILE		131.20	C ₆ H ₁₃ NO ₂
(S)2-Amino-4-methylpentanoic acid CAS# 61-90-5	L - Leucine	L - LEU		131.20	C ₆ H ₁₃ NO ₂
(S)-2,6-diaminohexanoic acid hydrochloride CAS# 657-27-2	L-Lysine Hydrochloride	L- LYH		182.65	C ₆ H ₁₄ N ₂ O ₂ ·HCl
(2)-2-amino-4-(methylsulphanyl)butanoic acid	L - Methionine	L - MET		149.2	C ₅ H ₁₁ NO ₂ S

CMC Review Data Sheet

CAS# 63-68-3 (S)-2-amino-3-phenylpropanoic acid CAS# 63-91-2	L-Phenylalanine	L - PHE		165.2	C ₉ H ₁₁ NO ₂
(S)-pyrrolidine-2-carboxylic acid	L - Proline	L - PRO		115.1	C ₅ H ₉ NO ₂
(S)-2-amino-3-hydroxypropanoic acid	L - Serine	L - SER		105.1	C ₃ H ₇ NO ₃
(2S,3R)-2-amino-3-hydroxybutanoic acid CAS# 72-19-5	L - Threonine	L - THR		119.1	C ₄ H ₉ NO ₃
(S)-2-Amino-3-(1H-indol-3-yl) propanoic acid CAS# 73-22-3	L-Tryptophan	L - TR or L-TRP		204.2	C ₁₁ H ₁₂ N ₂ O ₂
(S)-2-amino-3-(4-hydroxyphenyl) propanoic acid CAS# 16-80-4	L - Tyrosine	L - TYR		181.9	C ₉ H ₁₁ NO ₃
(S)-2-amino-3-methylbutanoic acid CAS# 72-18-4	L - Valine	L - VAL		117.1	C ₅ H ₁₁ NO ₂
mixture of variable proportions of sodium (2RS)-2,3-dihydroxypropyl phosphate & sodium 2-hydroxy-1-(hydroxymethyl) ethyl phosphate CAS # 1334-75-3	Sodium glycerophosphate (anhydrous), Ph.Eur.			216.0	C ₃ H ₇ Na ₂ O ₆ P, xH ₂ O
Calcium Chloride dihydrate, USP CAS # 10035-04-8				147.01	CaCl ₂ , 2H ₂ O
Magnesium Sulfate heptahydrate, USP				246.8	MgSO ₄ · 7H ₂ O
Potassium Chloride, USP				74.55	KCl
Sodium Acetate					C ₂ H ₃ NaO ₂ ·

CMC Review Data Sheet

trihydrate, USP (b) (4) Soyabean Oil, USP CAS # 8001-22-71	Dextrose, USP			136.08 198.2	3H ₂ O C ₆ H ₁₂ O ₆ ·H ₂ O
Egg Yolk Phospholipid (EYP)	None	EYP	Not established		

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	May-4-2014 Tarun Mehta	No major update since last review
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	May-19-2014	No major update since last review
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	May-4-2014 Tarun Mehta	No major update since last review
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	May-4-2014 Tarun Mehta	No major update since last review
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	May-4-2014 Tarun Mehta	No major update since last review

CMC Review Data Sheet

(b) (4)	(b) (4)				
	II	1	Adequate	May-4-2014 Tarun Mehta	No major update since last review
	II	1	Adequate	May-4-2014 Tarun Mehta	No major update since last review
	II	1	Adequate	May-4-2014 Tarun Mehta	No major update since last review
	II	1	Adequate	May-4-2014 Tarun Mehta	No major update since last review
	II	1	Adequate	May-4-2014 Tarun Mehta	No major update since last review
	IV	1	Adequate*	May-04-2014 Tarun Mehta	No major update since last review
	II	1	Adequate	May -09-2104	No major update since last review

¹ Action codes for DMF Table:

- 1 – DMF Reviewed.
- Other codes indicate why the DMF was not reviewed, as follows:
- 2 –Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available

* DMF is adequate as an excipient (b) (4) however, for this NDA, Egg yolk phospholipids is also used as an active ingredient as it contribute about (b) (4)% of phosphorus to the total label amount of phosphorous. The applicant has submitted information in the amendment 0012 dated 9/26/2011 (revised specification and validated methods), which is deemed adequate for the control of the phosphorus in the Egg yolk phospholipids.

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	May 22, 2014	Christina Capacci-Daniel
EA	Categorical exclusion is granted	May-5-2011	Tarun Mehta

The CMC Review for NDA 200656

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has issued an “*Acceptable*” recommendation for this application.

But, label/Labeling issues are not finalized as of this review.

Therefore, this NDA is not ready for APPROVAL from the ONDQA perspective in its present form per 21 CFR 314.125 (b)(6) pending finalized label/labeling .

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of CMC Assessments

A. Resolution of the Deficiencies noted in the Complete Response letter (11/21/2011), issues noted in the General Advice letters (7/26/2012, 7/31/2012), and Type C Meeting Minutes (10/25/13).

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

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

CMC Assessment Section

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

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

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

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

However, a leachable study was performed for the potential leaching of (b) (4) into the Kabiven infusion solution from the 3-CB on (b) (4) in conjunction with a (b) (4) for the NDA 17643 (Intralipid). The data showed that the highest level of (b) (4) leached out from the bags was (b) (4) µg/L. Initially the reported level posed a safety concern from the toxicology perspective, but upon taking into account the (b) (4) exposure to human in indoor and outdoor air, drinking water, groundwater, surface water, soil, and food, it was decided that the estimated worst case exposure from Intralipid would be (b) (4) µg/day and it would not be considered as a major safety concern. Therefore, the same (b) (4) used in Kabiven /Perikabiven IV products for this NDA are considered to pose no safety concern from the potential leachables/extractables (see Pharm/tox Review by Emmanuel Akinshola, dated 5/13/2014).

- A new supplier for (b) (4) was proposed for Kabivan and Perikabivan, and based on the review for DMF (b) (4), it is deemed adequate for these drug products.
- The ONDQA Precedence Committee held on May 13, 2014 had decided that there are no active moiety which could be designated as an NME in the drug product of this NDA. However, organic glycerol phosphate (Sodium Glycerophosphate) used as an active ingredient to supply phosphate will be consider new active ingredient.

B. Basis for Not Approval Recommendation:

21 CFR 314.125(b)(6)

- Labels/labeling issues are not resolved.

CMC Assessment Section

(See the **List of Deficiencies** on p. 56)

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Tarun Mehta, M.Sc.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch III/DPA II, ONDQA

C. CC Block: entered electronically in DFS

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/s/

TARUN D MEHTA
05/22/2014

MOO JHONG RHEE
05/22/2014
Chief, Branch IV

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 200656/000
Code: 180
Priority: 1
Stamp Date: 28-JAN-2011
PDUFA Date: 25-MAY-2014
Action Goal:
District Goal: 26-MAR-2014

Sponsor: FRESENIUS KABI USA
 3 CORPORATE DR
 LAKE ZURICH, IL 60047
Brand Name: KABIVEN AND PERIKABIVEN
Estab. Name:
Generic Name: (b) (4)
Product Number; Dosage Form; Ingredient; Strengths
 (b) (4)

FDA Contacts:	T. MEHTA	Prod Qual Reviewer		3017961712
	D. MILLER	Micro Reviewer	(HFD-003)	3017963854
	C. TRAN-ZWANETZ	Product Quality PM	(HFD-800)	3017963877
	R. ISHIHARA	Regulatory Project Mgr	(HFD-180)	3017960069
	M. KOWBLANSKY	Team Leader		3017961390

Overall Recommendation:	ACCEPTABLE	on 22-MAY-2014	by C. CAPACCI-DANIEL ()	3017963532
	PENDING	on 07-MAY-2014	by EES_PROD	
	PENDING	on 07-FEB-2014	by EES_PROD	
	PENDING	on 31-DEC-2013	by EES_PROD	
	PENDING	on 30-DEC-2013	by EES_PROD	
	PENDING	on 30-DEC-2013	by EES_PROD	
	PENDING	on 16-DEC-2013	by EES_PROD	
	PENDING	on 16-DEC-2013	by EES_PROD	
	PENDING	on 16-DEC-2013	by EES_PROD	
	PENDING	on 13-DEC-2013	by EES_PROD	
	PENDING	on 19-JUN-2013	by EES_PROD	
	PENDING	on 19-JUN-2013	by EES_PROD	
	WITHHOLD	on 12-JUN-2012	by EES_PROD	
	PENDING	on 10-MAY-2012	by EES_PROD	
	WITHHOLD	on 20-DEC-2011	by EES_PROD	
	PENDING	on 20-DEC-2011	by EES_PROD	
	WITHHOLD	on 20-DEC-2011	by EES_PROD	
	WITHHOLD	on 28-NOV-2011	by EES_PROD	
	WITHHOLD	on 28-NOV-2011	by EES_PROD	
	WITHHOLD	on 21-NOV-2011	by EES_PROD	
	PENDING	on 15-NOV-2011	by EES_PROD	
	WITHHOLD	on 04-NOV-2011	by EES_PROD	
	WITHHOLD	on 20-JUL-2011	by EES_PROD	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

WITHHOLD

on 18-MAR-2011 by EES_PROD

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-APR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-DEC-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)
DMF No: [REDACTED] **AADA:**
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-JUL-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)
DMF No: [REDACTED] **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: [REDACTED] (b) (4) **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-JUL-2012
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)
DMF No: [REDACTED] **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-JUL-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9691024 FEI: 3002996654
FRESENIUS KABI (BRUNNA FACILITY) AB
KRAFTVAGEN 1
KUNGSANGEN, , SWEDEN

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9614128 FEI: 3002631703
FRESENIUS KABI AB
RAPSGATAN 7
UPPSALA, , SWEDEN

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE MANUFACTURER

Profile: LARGE VOLUME PARENTERALS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)
DMF No: [REDACTED] **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-MAY-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)
DMF No: [REDACTED] **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
Profile: NON-STERILE API [REDACTED] (b) (4) **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-MAY-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)
DMF No: [REDACTED] **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
Profile: NON-STERILE API [REDACTED] (b) (4) **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-MAY-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-JUL-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-JUN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-JUL-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-JUL-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-DEC-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

MEMORANDUM

Date: November 8, 2011

To: NDA 200-656

From: Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for “Complete Response” for NDA 200-656, Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose (Kabiven™ and (b) (4))

I have assessed the ONDQA reviews of NDA 200-656 by Tarun Mehta, Ph.D. The initial ONDQA CMC review was entered into DARRTS on September 28, 2011, with a recommendation for a Complete Response due to deficiencies associated with DMF (b) (4) for (b) (4), (b) (4), lack of purity assurance and adequate controls of heavy metals for the drug product, the “Withhold” recommendation from the Office of Compliance on the manufacturing and testing sites acceptability, and pending labeling issues.

Kabiven and (b) (4) are sterile parenteral nutrition products, each comprising of (b) (4) drug substances representing seventeen amino acids, (b) (4) electrolytes, glucose monohydrate, and purified soybean oil. The products are designed so that the dextrose solution, amino acid and electrolyte solution and fat emulsion are contained in separate chambers of a flexible clear (b) (4) bag. Prior to administration, the seals between the chambers are broken and the three fluids are allowed to mix. The volume of fluid is delivered through a single IV port. Kabiven is manufactured in four packaging sizes: 1026 ml, 1540 ml, 2053 ml, and 2566 ml; (b) (4) is manufactured in three sizes: 1440 ml, 1920 ml and 2400 ml.

On July 12, 2011 the Office of Compliance entered an Overall Recommendation of “Withhold” into EES. This recommendation was updated on November 04, 2011, with the same overall recommendation. The Product Quality Microbiology Review, by Denise Miller, entered into DARRTS on September 21, 2011 recommends “to approve from a quality microbiology standpoint”. An ONDQA Biopharmaceutics review was not performed for this NDA.

An amendment to the ONDQA CMC review was entered into DARRTS on November 08, 2011, in regards to a November 04, 2011 teleconference between the ONDQA CMC review team and the applicant in response to a memo sent by the applicant on November 01, 2011. APP described their ongoing stability program in which four of the nine pivotal batches demonstrated results above the acceptance limit for particulate matter. APP identified the particles present in the lipid chamber of the IV bag as (b) (4). The particles are thought to be caused by migration of components from the stopper.

Based on the data submitted to the NDA and the above teleconference, an expiration dating period for the product has not been established. The FDA agreed that a (b) (4)-month expiration period may be acceptable if data from additional studies, including refrigerated conditions, support the period. It is expected that this data will be reviewed in the next review cycle.

The Drug Master Files (DMF) (b) (4) were reviewed for the drug substances utilized for this NDA and were found to be “Adequate” to support this NDA. However, the DMF for the drug substance (b) (4) (DMF (b) (4)) was found to be “Inadequate” by Dr. Mehta to support this NDA. Of interest for this NDA, egg phospholipid, which is commonly used as an excipient, is treated as a drug substance due to its contribution of phosphate to the drug product. This DMF (DMF (b) (4)) was found “Adequate” to support NDA 200-656.

Secondary review of the CMC reviews was performed by Moo-Jhong Rhee, Ph.D.

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/s/

TERRANCE W OCHELTRIE
11/08/2011

MEMORANDUM

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

DATE: November 08, 2011
TO: Review #1 of NDA 200656
FROM: Tarun Mehta, M.Sc.
Review Chemist, ONDQA
SUBJECT: **Revised Expiration Dating Period.**

1. SUMMARY

The Review #1 indicated that the proposed 24-month expiration dating period is acceptable based on the submitted 24 months real time stability data.

However, the applicant had submitted the memo via email dated November 01, 2011 notifying the out of specification results for the limit of particulate matter in their stability batches.

The applicant states in the memo that,
“The Kabiven and (b) (4) drug product’s out of specification (OOS) results for the limit of particulate matter (according to USP <788>) have been obtained for four of the nine pivotal batches submitted at test point 24 months. Up to 12 months all results for particulate matter were within specification for all nine batches. Three of the pivotal batches are still ongoing. Additional testing for particulate matter was recently performed on these three batches (after 16 months storage), were results above specification were obtained for one of them.”

The applicant had investigated the probable root cause of these OOS results and found:

1. The particles were found only in the chamber containing lipid emulsion.
2. The particles were characterized using FTIR and SEM-DEX showing that they consist of fatty acid and (b) (4), most likely (b) (4).
3. The source of the (b) (4) is believed to be leached from the stopper, and fatty acids (of varying carbon chains including stearic acid) are derived from the hydrolysis of the lipid constituents of the soybean oil emulsion.

Based on the finding and root-cause analysis, the applicant commits to implement the following corrective actions:

1. Fresenius Kabi will implement a modified stopper to reduce the amount of (b) (4).

2. New stability batches of Kabiven and (b) (4) using the newly identified stopper with reduced (b) (4) content will be manufactured and put upon stability. Stability testing will be performed in accordance with the stability protocol used for the ongoing study with the addition that the particulate matter in the emulsion will be analyzed at each testing point.

Upon request from the applicant, a teleconference was held between FDA and the applicant on 11/04/11, and the following points were discussed.

APP proposed the following commitments regarding the drug product shelf life: Although the target expiration dating period was aimed for 24 months when stored not above 25°C in the pivotal stability studies, because of the formation of (b) (4), APP suggests (b) (4). If corrective actions are implemented, the expiration dating period will be reverted to 24 months.

The following is the agreements made between FDA and the sponsor: (memo Reference ID: 3039983):

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

2. Conclusion/ Recommendation:

This newly provided information does not affect the previous recommendation of “**Not Approval**” stated in the Review #1.

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/s/

TARUN D MEHTA

11/08/2011

This review is an amendment (Memo) to complete CMC review # 1

MOO JHONG RHEE

11/08/2011

Chief, Branch IV

NDA 200-656

Kabiven™ and [REDACTED] ^{(b) (4)} (pending)
Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose (pending)

APP Pharmaceuticals.
(a company of the Fresenius Kabi Group)

Tarun Mehta

Review Chemist

Division of New Drug Quality Assessment II
Premarketing Branch IV
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 200-656
For the Division of Gastroenterology Products (HFD-180)

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 200-656
2. REVIEW #: 1
3. REVIEW DATE: 26-Sept-2011
4. REVIEWER: Tarun Mehta
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	January/31/ 2011
Amendment 0001	March/10/ 2011
Amendment 0002	April/06/2011
Amendment 0003	April/25/2011
Amendment 0004	May/10/2011
Amendment 0007	July/27/2011
Amendment 0011	September/7/2011
Amendment 0012	September/16/2011

7. NAME & ADDRESS OF APPLICANT:

Name: APP Pharmaceutical, LLC (a company of the Fresenius Kabi Group)
 Address: 1501 East Woodfield Road, Suite 300E
 Schaumburg, IL 60173
 Representative: Aparna Dagar, Ph.D.
 Telephone: (847) 969-2706

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kabiven™ and (b) (4) pending
- b) Non-Proprietary Name: Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose pending
- c) Code Name/# (ONDQA only): None
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 1

CMC Review Data Sheet

- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Total parenteral nutrition

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: (b) (4) kcal/L and (b) (4) kcal/L

13. ROUTE OF ADMINISTRATION: Intravenous infusion

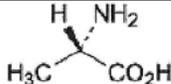
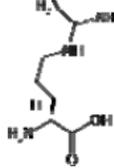
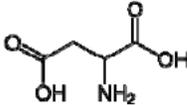
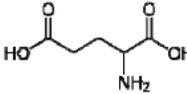
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed

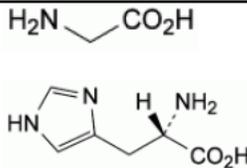
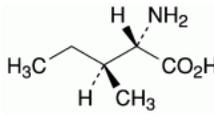
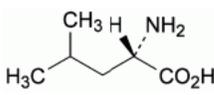
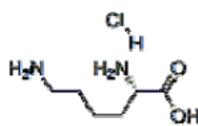
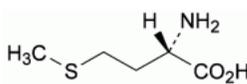
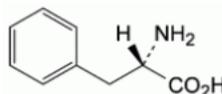
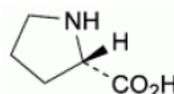
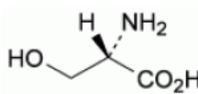
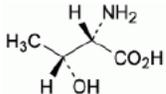
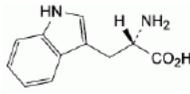
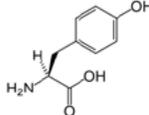
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical names, compendial names, structural formulas, abbreviations for active ingredients:

Chemical Name	INN name	Abbreviation	structural formula	MW g/mol	MF
(S)-2-Aminopropanoic acid CAS # 56-41-7	L- Alanine	L-ALA		89.1	C ₃ H ₇ NO ₂
(S)-2-amino-5-guanidinopentanoic acid CAS# 74-79-3	L-Arginine	L-ARF		174.20	C ₆ H ₁₄ N ₄ O ₂
(2S)-2-aminobutanedioic acid CAS# 56-84-8	L- Aspartic Acid	L- ASP		133.10	C ₄ H ₇ NO ₄
(2S)-2-aminopentanedioic acid CAS# 56-86-0	L-Glutamic Acid	L - GA		147.1	C ₅ H ₉ NO ₄
2-Aminoacetic acid	Glycine	Gly		75.1	C ₂ H ₅ NO ₂

CMC Review Data Sheet

CAS# 56-40-6 (S)-2-Amino-3-(imidazol-4-yl)propanoic acid CAS# 71-00-1	L- Histidine	L-HISF		155.2	C ₆ H ₉ N ₃ O ₂
(2S,3S)-2-Amino-3-methylpentanoic acid CAS# 73-32-5	L - Isoleucine	L - ILE		131.20	C ₆ H ₁₃ NO ₂
(S)-2-Amino-4-methylpentanoic acid CAS# 61-90-5	L - Leucine	L - LEU		131.20	C ₆ H ₁₃ NO ₂
(S)-2,6-diaminohexanoic acid hydrochloride CAS# 657-27-2	L-Lysine Hydrochloride	L- LYH		182.65	C ₆ H ₁₄ N ₂ O ₂ ·HCl
(2)-2-amino-4-(methylsulphonyl)butanoic acid CAS# 63-68-3	L - Methionine	L - MET		149.2	C ₅ H ₁₁ NO ₂ S
(S)-2-amino-3-phenylpropanoic acid CAS# 63-91-2	L-Phenylalanine	L - PHE		165.2	C ₉ H ₁₁ NO ₂
(S)-pyrrolidine-2-carboxylic acid	L - Proline	L - PRO		115.1	C ₅ H ₉ NO ₂
(S)-2-amino-3-hydroxypropanoic acid	L - Serine	L - SER		105.1	C ₃ H ₇ NO ₃
(2S,3R)-2-amino-3-hydroxybutanoic acid CAS# 72-19-5	L - Threonine	L - THR		119.1	C ₄ H ₉ NO ₃
(S)-2-Amino-3-(1H-indol-3-yl) propanoic acid CAS# 73-22-3	L-Tryptophan	L - TR or L-TRP		204.2	C ₁₁ H ₁₂ N ₂ O ₂
(S)-2-amino-3-(4-hydroxyphenyl)propanoic acid CAS# 16-80-4	L - Tyrosine	L - TYR		181.9	C ₉ H ₁₁ NO ₃
(S)-2-amino-3-methylbutanoic acid	L - Valine	L - VAL		117.1	C ₅ H ₁₁ NO ₂

CMC Review Data Sheet

(b) (4)	(b) (4)	3	Adequate	May-20-2009	Reviewed by Zedong Dong No update since last review
(b) (4)	(b) (4)	1	Adequate	May-5-2011 Tarun Mehta	No update since last review
(b) (4)	(b) (4)	1	Adequate	May-5-2011 Tarun Mehta	No update since last review
(b) (4)	(b) (4)	1	Adequate	May-5-2011 Tarun Mehta	No update since last review
(b) (4)	(b) (4)	1	Adequate	May-5-2011 Tarun Mehta	No update since last review
(b) (4)	(b) (4)	1	Adequate	May-5-2011 Tarun Mehta	No update since last review
(b) (4)	(b) (4)	1	Adequate	May-5-2011 Tarun Mehta	No update since last review
(b) (4)	(b) (4)	1	Adequate	May-5-2011 Tarun Mehta	No update since last review
(b) (4)	(b) (4)	1	Inadequate	August 30, 2011	
(b) (4)	(b) (4)	3	Adequate*	Feb-11-2008 Review by Huai T. Chang	No update since last review

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

CMC Review Data Sheet

* DMF is adequate as an excipient (b) (4) however, for this NDA, Egg yolk phospholipids is also used as an active ingredient as it contribute about (b) (4) of phosphorus to the total label amount of phosphorous. The applicant has submitted information in the amendment 0012 dated 9/26/2011 (revised specification and validated methods), which is deemed adequate for the control of the phosphorus in the Egg yolk phospholipids.

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None**18. STATUS:****ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Withhold	July 12, 2011	
EA	Categorical exclusion is granted	May-5-2011	Tarun Mehta

Executive Summary Section

The CMC Review for NDA 200-656

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has *not* provided sufficient information to assure the *purity* of the drug product.

The Office of Compliance has issued a **WITHHOLD** recommendation for this application.

Label/Labeling issues are still pending.

Therefore, per 21CFR 314.125(b)(1),(6),(13), this NDA is not recommended for approval in its present form until all the pending issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substances

Kabiven and (b) (4) each contains a total of (b) (4) drug substances: seventeen amino acids, (b) (4) electrolytes, glucose monohydrate, and purified soybean oil.

All amino acids are prepared either by (b) (4). All conform to USP requirements, with the exception of glutamic acid, which conforms to the European Pharmacopoeia (*Ph.Eur.*). Manufacturing information regarding these amino acids is referenced to DMFs, all of which have been found acceptable, except for the DMF (b) (4) for (b) (4) of which purity issue has not been resolved. The stability data have justified a (b) (4)-month re-test periods for all amino acids.

Executive Summary Section

The electrolytes are inorganic salts, with two exceptions: sodium glycerophosphate (SGP), which is manufactured by (b) (4), and egg phospholipids which is an egg extract. Both are sources of phosphorous in this total parenteral nutrition (TPN) product. Sodium glycerophosphate is commercially available, with a monograph in Ph.Eur. However, this will be the first use of this material in the U.S. as an active ingredient in a pharmaceutical preparation; consequently, it is considered a new molecular entity (NME). Egg phospholipids has been extensively used as an excipient ((b) (4)) in parenteral lipid nutrition products, but in the current product this material also functions as an active ingredient since it contributes to the labeled phosphorous content of the product, along with the glycerophosphate. Because this is the first use of egg phospholipids as an active ingredient, it is also classified an NME.

The manufacturing process for the inorganic electrolytes involves (b) (4). All inorganic electrolytes that constitute this product meet USP monograph requirements.

Glucose conforms to USP requirements. CMC information regarding the manufacture of this material is referenced to DMF (b) (4), which has been found to be acceptable.

Purified soybean oil is a USP monograph material. It is a mixture of triglycerides ((b) (4) fatty acids, palmitic acid ((b) (4)), oleic acid ((b) (4)) and linoleic acid ((b) (4)). Manufacture and controls are described directly in the submission.

Based on the information submitted, all proposed active ingredients, except for the (b) (4) (DMF (b) (4)), which is based on an alternate supplier, are judged acceptable for use in the proposed products.

(2) Drug Products

The current NDA is for two drug products, Kabiven and (b) (4), which are sterile parenteral nutrition products intended for intravenous administration: Kabiven, via an (b) (4) central vein, and (b) (4), via a peripheral or central vein. Kabiven is manufactured in four packaging sizes: 1026 ml, 1540 ml, 2053 ml, and 2566 ml; (b) (4) is manufactured in three sizes: 1440, 1920 and 2400 ml. Both products are manufactured as a three-chamber bag.



Executive Summary Section

One chamber contains a fat emulsion (soybean oil); another, an aqueous solution of seventeen amino acids with five electrolytes; and the third, an aqueous glucose solution. (As mentioned above, egg phospholipids from the emulsion compartment contributes phosphorous to the electrolyte content of this product.) The chambers are separated by peelable seals that are internally opened to each other at the time of use, resulting in the formation of a single large chamber where the contents of the three chambers mix. According to the applicant, storing the nutrients in separate chambers improves the chemical stability of the individual components and improves the physical stability of the fat emulsion. The composition of the amino acid chamber is identical in both products, as is the composition of the fat emulsion chamber; the glucose chamber, however, differs between the two products, as Kabiven and (b) (4) contains (b) (4)% and (b) (4)% of glucose, respectively. It should be noted that the fat emulsion chamber is filled with an FDA-approved product that is marketed by Fresenius Kabi as Intralipid® 20%. (Fresenius Kabi will also be manufacturing the current product.)

The manufacturing process consists of: (b) (4)

(b) (4) . The submission notes that (b) (4)% of the (b) (4) is (b) (4) to (b) (4) and (b) (4) during the (b) (4)

Specification for each of the three chambers is adequately established, and the stability testing is conducted for each of the chamber individually. The glucose chamber is tested for conformance to the USP monograph for Dextrose. The amino acid chamber is analyzed for the individual amino acids, as well as sodium, potassium, calcium, magnesium and phosphorous content The fat emulsion chamber is tested in accord with recommendations for Lipid Injectable Emulsions, testing for triglycerides, glycerol, phospholipids, free fatty acids, pH, and USP <729> for globule size/distribution.

The mixed product (mixed bag) specification is adequate. It meets USP requirements, with testing for traces of aluminum, sterility, endotoxins, and mean globule size and globule size distribution as recommended in USP <729>. Globule size is a critical attribute that can affect the safe use of this type of product.

However, the heavy metal content in the drug product was monitored only for the individual drug substances per USP, but no test and acceptance criterion is given for individual chamber or for the whole mixed chamber product. Since the drug product daily dose is very large ((b) (4) mL to 2556 mL), the cumulative amount of heavy metals can easily surpass the daily allowable limits, and, therefore, applicant should revise the drug product specification to include the tests and limits for the heavy metals. The specific heavy metals and their limits will be determined after data are collected.

Therefore, the drug product specification is deemed **inadequate** due to the absence of controlling the heavy metals.

Executive Summary Section

The submitted data support the proposed 24-month expiration dating period for the product stored at room temperature. The applicant has also provided adequate stability data including additional 24 hours at ambient condition to support the label claim that the product may be stored under refrigerated conditions for 24 hours after being mixed.

The proposed **established name** “(b) (4)” is **not acceptable as it does not take into account all the types of active substances that are present in the product**. By analogy to other USP TPN products, the following is recommended as an established name:

“Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose”

However, the applicant has submitted the following revised established name in amendment No.: 0010 (8/18/2011):

(b) (4)

which is deemed **not acceptable**.

B. Description of How the Drug Product is Intended to be Used

The drug product is (b) (4)

C. Basis for Not-Approval Recommendation

1. 21CFR 314.125(b)(1)

- The applicant has **not** provided adequate controls for the heavy metals in the drug product. Due to the large volumes of the drug product to be infused into patients, it is deemed critical to control the amount of daily intake of the heavy metals. They should be adequately controlled by the **specification** with proper method and adequate acceptance criteria.
- The applicant has **not** provided adequate controls for the impurities in (b) (4), which is one of the drug substances in the drug product.
- The applicant has not provided sufficient information on the container/closure system in terms of adequacy for food additive requirements.

2. 21CFR 314.125(b)(13)

- The Office of Compliance has issued an overall **“Withhold”** recommendation for the application

Executive Summary Section

3. 21CFR 314.125(b)(6)

- Labels/labeling do *not* have an adequate information including the established name.

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Tarun Mehta, M.Sc.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch III/DPA II, ONDQA

C. CC Block: entered electronically in DFS

67 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/

TARUN D MEHTA
09/27/2011

MARIE KOWBLANSKY
09/28/2011

MOO JHONG RHEE
09/28/2011
Chief, Branch IV

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology Products
NDA: 200-656
Applicant: APP Pharmaceuticals
Stamp Date: 1/31/2011
Review Date: 2/28/2011
PDUFA Date: 11/28/2011
Filing Meeting: 3/23/2011
Proposed Trademark: Kabiven™ and (b) (4)
Established Name: (b) (4)
Dosage Form: (b) (4)
Route of Administration: intravenous
Indication: total parenteral nutrition

PAL: Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

A. Summary

Kabiven™ (b) (4) and (b) (4) are sterile total parenteral nutrition products intended to be a source of calories, protein, and essential fatty acids for patients. Each product contains a total of (b) (4) drug substances: seventeen amino acids, five electrolytes, glucose (dextrose), and soybean oil. Both Kabiven and (b) (4) are intended for intravenous administration: Kabiven via an (b) (4) central vein and (b) (4) via a peripheral or central vein. This single 505(b)(2) application has been submitted for both products, in agreement with FDA's advice letter dated January 2010 (under PIND 105,282). The reference listed products are

- Intralipid (NDAs 18-449 and 20-248)
- Novamine Injection 11.4% (NDA 17-957)
- Aminosyn II with Electrolytes in Dextrose Injection with calcium (NDA 19683)
- Clinimix E Sulfite free with Electrolytes in Dextrose with calcium (NDA 20-678)

Since this product is a new combination of active ingredients, according to the Chemical Classification Code, MAPP 7500.3 this is classified as a Type 4 application.

Drug Substances

Kabiven and (b) (4) are composed of (b) (4) drug substances:

Amino acids (17): L-alanine, L-arginine, L-aspartic acid, L-glutamic acid, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine hydrochloride, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, and L-valine. All conform to USP requirements, with the exception of glutamic acid, which conforms to the European Pharmacopoeia (*Ph.Eur.*). All manufacturing information regarding these amino acids is referenced to DMFs.

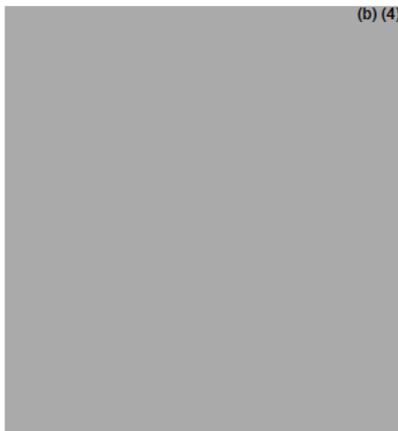
Electrolytes (5): calcium chloride dihydrate, magnesium sulphate heptahydrate, potassium chloride, sodium acetate trihydrate, sodium glycerophosphate, (b) (4). The first four conform to the USP monograph; sodium glycerophosphate conforms to *Ph.Eur.* Manufacturing procedures for each are described directly in the submission; no DMFs are referenced

Glucose (dextrose): Conforms to the USP monograph for Dextrose Injectable. CMC information regarding the manufacture of this material is referenced to DMF (b) (4).

Soybean oil, USP: purified soybean oil is a mixture of triglycerides (b) (4) fatty acids, palmitic acid (b) (4), oleic acid (b) (4) and linoleic acid (b) (4). Manufacture and controls are described directly in the submission.

Drug Product

Both Kabiven and (b) (4) are designed to be marketed in a three-chamber plastic bag:



One chamber contains a fat emulsion; another, an aqueous amino acid solution with electrolytes; and the third, an aqueous glucose solution. The chambers are separated by peelable seals that are opened at the time of use, resulting in the formation of a single large compartment where the contents of the three compartments mix. It should be noted that the fat emulsion compartment is an FDA-approved product that is marketed by Fresenius Kabi as Intralipid® 20%. (Fresenius Kabi will also be manufacturing the current product.) According to the applicant, storing the nutrients in separate chambers improves the chemical stability of the individual components and improves the physical stability of the fat emulsion.

The 3-compartment bag is manufactured (b) (4).

The bag is (b) (4).

(b) (4) Fill volume is an in-process control. Kabiven will be manufactured in four packaging sizes: 1026 ml, 1540 ml, 2053 ml, and 2566 ml; (b) (4)

(b) (4) will be manufactured in three sizes, 1440, 1920 and 2400 ml. The qualitative and quantitative composition of the amino acid compartment is identical in both products, as is the composition of the fat emulsion compartments; the glucose compartment, however, differs between the two products, containing (b) (4) % glucose in Kabiven and (b) (4) % in (b) (4).

When the compartments are mixed, the concentrations of glucose, amino acids, and electrolytes in the (b) (4) are (b) (4) % of the concentrations in the Kabiven; the lipids concentration in the mixed (b) (4) is approximately (b) (4) % of the mixed concentration in Kabiven.

Other ingredients in the formulation include water for injection, glacial acetic acid, nitrogen, purified egg phospholipids, (b) (4), and sodium hydroxide; again all are NF/USP except purified egg phospholipids. The purified egg phospholipids are of (b) (4). However,

according to the submission, the purified egg phospholipids (b) (4)

Manufacture of solutions for the glucose and amino acid plus electrolytes chambers involve (b) (4)

The purified soybean oil emulsion is prepared through (b) (4)

Specifications for release and stability testing are defined for each of the compartments individually:

glucose compartment: Tested according to the USP monograph for Dextrose Injection, which includes testing for (b) (4) which may be formed during (b) (4) and storage. Additionally, testing for pH (USP), color (Ph. Eur), and particulate matter (USP) are performed.

amino acids with electrolytes compartment: The amino acids analyzed individually. They are separated by cation-exchange-chromatography, post-column derivatized with ninhydrin, and detected spectrophotometrically at 440 nm and 570 nm. Sodium and potassium are determined by flame emission spectrophotometry, calcium and magnesium by atomic absorption. Phosphorous is quantitated colorimetrically after forming a vanadium-molybdenum complex.

fat emulsion compartment: Testing is for triglycerides, (b) (4) phospholipids, and free fatty acids. The free fatty acids are hydrolysis products, and the ^w% limit is the same as for (b) (4), which is a USP product. Also tested are droplet size and pH.

In addition, all compartments are tested for particulate matter using USP procedures.

The mixed bag is tested for sterility, endotoxins, and aluminum content.

Stability: Up to twelve months of controlled room temperature stability data and six months of accelerated data have been submitted, with a request for 24-month expiration dating. A bracketing and matrixing design was used in the stability studies, with the largest and smallest container sizes for both Kabiven and (b) (4) being included in the testing. Based on this current initial evaluation, no trends indicative of instability are apparent in the data. The fatty acid content, for example, increases only modestly over the course of the study, going from 0.5 mM to 1.8 mM after 12 months of room temperature storage, and up to 3.7 mM after 6 months at 40°C (the specification limit is ^w mM).

In accordance with 21 CFR 25.31(c), Fresenius Kabi claims categorical exclusion from an environmental assessment on the basis that the substances in this product occur naturally in the environment and approval of the product will not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. As of the date of this review, the district office has issued Withhold recommendations for two of the facilities.

Established name: The proposed names for these related products are Kabiven™ (b) (4) and (b) (4).

Reviewers: The CMC review for this application has been assigned to Tarun Mehta.

Consults: Because of the three-compartment design of the bag, A formal Consult will be requested from CDRH.

Microbiology: The microbiology staff will review issues related to product sterility.

B. Critical issues for review

Fresenius Kabi, has extensive experience manufacturing these types of products and consequently has prepared what looks like a well documented submission (although several contacts were required with the company to obtain a complete and accurate list of manufacturing sites). The following issues may require particular consideration by the reviewer:

- The purified egg phospholipids are (b) (4). Measures need to be taken to ensure that appropriate testing for this type of material is conducted. (It may be helpful to refer to the Intralipid NDAs mentioned above.) A consult may be required to ensure that there is no viral contamination from this excipient.
- Attention should be given to the plastic bag that is used for this product. In addition to general USP <661> requirements with regard to leachables, attention should be directed to ensuring that product specific compatibility with the (b) (4) container has been evaluated, including the sealable strips that separate the individual compartments.
- The specification requires that the contents of the mixed bag be tested for aluminum content (< (b) (4) µg/mL). USP requires labeling that states that the product "Contains no more than 25 µg/L of aluminum". Thus this limit must be met at expiry.
- According to USP <729> globule size and distribution need to be controlled within specified limits, since globule size is related to infusion safety. Although the globule size is controlled in the individual lipid compartment, there is no testing of globule size for the mixed solution. Consideration should be given as to whether this should be required.
- The proposed name is Kabiven™ (b) (4) and (b) (4) (b) (4). Consideration should be given as to what the correct established name should be.

C. Comments for 74-Day Letter --

None

D. Recommendation – From the CMC perspective this application may be filed

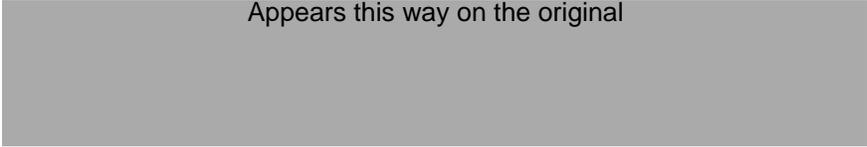
Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

3/23/2011

Moo-Jhong Rhee, PhD
Branch Chief

3/23/2011

Appears this way on the original



FILING CHECKLIST

NDA Number: NDA 200-656 **Supplement Number and Type:** original **Established/Proper Name:** Total parenteral nutrition

Applicant: APP Pharmaceuticals. **Letter Date:** October 15, 2010 **Stamp Date:** 1/31/2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		As amended
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		As amended

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	√		Claim of categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	√		DMFs referenced
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		DMFs referenced
14.	Does the section contain information regarding the characterization of the DS?	√		DMFs referenced
15.	Does the section contain controls for the DS?	√		DMFs referenced
16.	Has stability data and analysis been provided for the drug substance?	√		DMFs referenced
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?		√	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	√		Included in submission

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	√		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	√		

{See appended electronic signature page}

Marie Kowblansky, Ph.D.
 CMC Lead
 Division of Pre-Marketing Assessment 2, Office of New Drug Quality Assessment

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Branch Chief
 Division of Pre-Marketing Assessment 2, Office of New Drug Quality Assessment

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

/s/

MARIE KOWBLANSKY
03/24/2011

MOO JHONG RHEE
03/24/2011
Chief, Branch IV