

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204508Orig1s000**

**CHEMISTRY REVIEW(S)**

**MEMORANDUM**

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

**DATE:** October 2, 2013  
**TO:** Review #1 of NDA 204508, dated June 20, 2013  
**FROM:** Tarun Mehta, M.Sc.  
Review Chemist, ONDQA  
**SUBJECT:** **Final Approval Recommendation.**

The CMC Review #1 dated June 20, 2013 has noted the following deficiencies, and now all the outstanding issues are resolved as follows:

**A. Regarding the Drug Product**

**Deficiency 1:**

*The drug product specification needs to be revised according to ICH Q3D and EMEA guidance for elemental impurities in LVP (large volume parenteral).*

**Response:**

Based on the data submitted on June 25, 2013 in amendment 0012 for the elemental analysis for all three registration batches and upon FDA request, Baxter has agreed to introduce such testing specification in a CBE-0 supplement, as they indicated in their May 6, 2013 amendment to the NDA. See below:

**“To ensure timely notification to the FDA Baxter proposes a CBE-O submission prior to the launch. The updated sections of the eCTD, including new specifications, procedures, validation, Master Production Records for our Lessines facility, etc. would be submitted in the CBE-O”.**

Table below summarizes the anticipated human daily exposure (HDE, ug/day) to each of the elemental impurities within the scope of the FDA’s request in relation to established, or proposed daily intakes, from the ICH or EMEA.

Table: Summary of Elemental Impurities Risk Assessment:

(b) (4)



QL = Quantitation limit for the standards prepared on the day of analysis.

HDE = Human Daily Exposure

PDE = Permissible Daily Exposure. Reference 2.

<sup>1</sup> Testing was performed on three units from each of the 3 respective primary stability batches manufactured in support of NDA 204508. Reference 8. No values were observed above the QL.

<sup>2</sup> Calculated as  $[(QL \text{ (ng/mL)} \times 625 \text{ mL/day}) / (1000 \text{ ng/}\mu\text{g})]$

**The response is satisfactory.**

**Deficiency 2:**

*The DMF (b) (4) (Clarity container closure system) was not deemed adequate per CDRH consult review.*

**Response:**

Now CDRH reviewer, Jason To indicated that the proposed device now appears to be acceptable with respect to device performance testing. (See the Review dated August 01, 2013)

**The response is satisfactory.**

**B. Regarding Label/Labeling**

**Deficiency 3:**

*The drug product label/labeling are not finalized as of this review.*

**Response:**

The applicant has resolved the CMC's labeling issues via email response dated September 23, 2013. (see the **Attachment-2**)

**The response is satisfactory.**

**C. Regarding the Inspection of Facilities**

**Deficiency 4:**

*The Office of compliance has not issued an overall "Acceptable" recommendation for the facilities involved in this application.*

**Response:**

The Office of compliance has issued an overall "Acceptable" recommendation on September 23, 2013 for all the facilities involved in this application. (see the **Attachment-1**)

**The response is satisfactory.**

**Final Recommendation:**

From the ONDQA perspective, this NDA is now recommended for **APPROVAL** with an expiration dating period of 18 months and PMR/PMC as detailed in the **Attachment-3**.

# Attachments:

## Attachment-1:

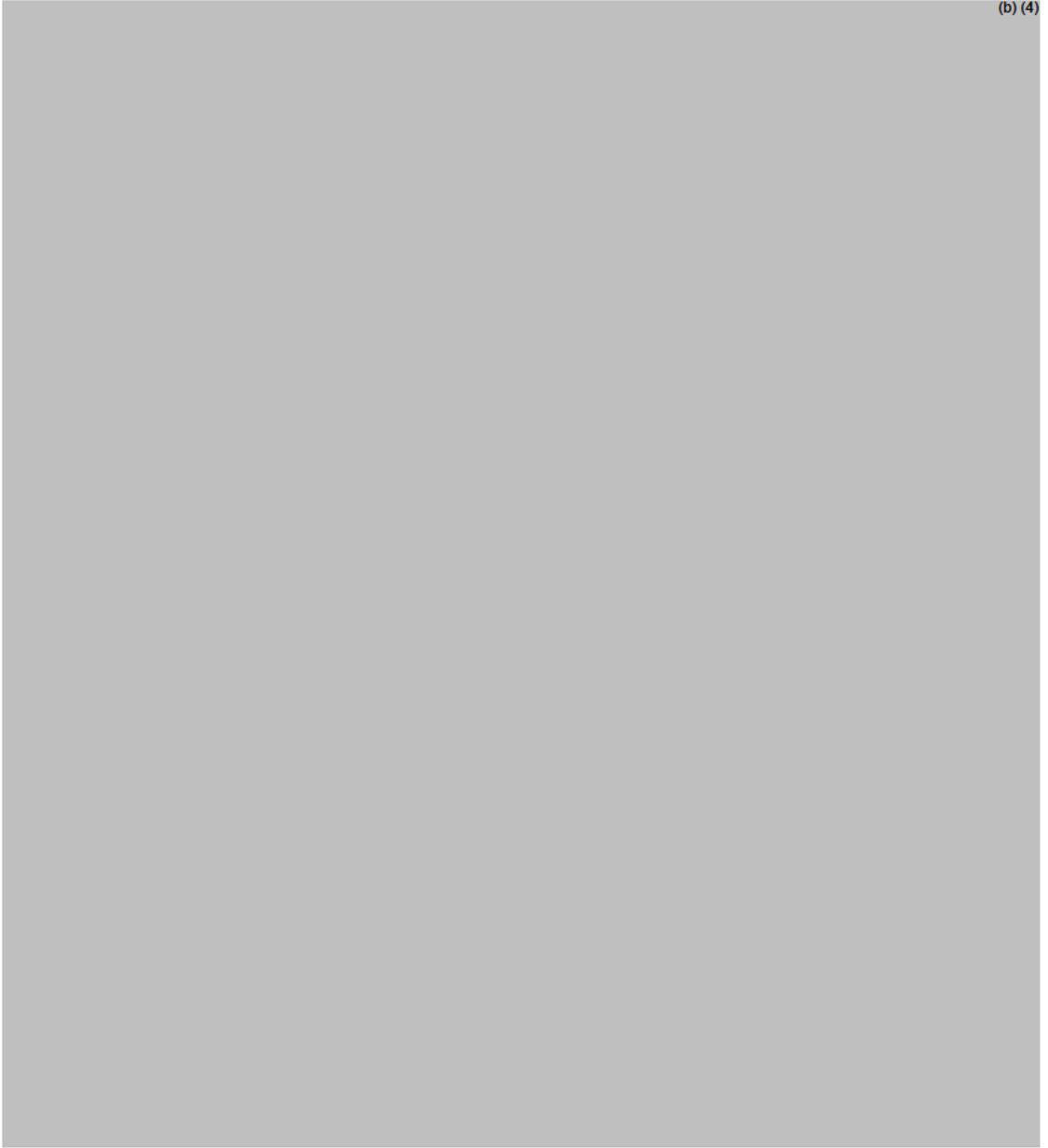
### EES Report:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT					
<b>Application:</b>	NDA 204508/000	<b>Sponsor:</b>	BAXTER		
<b>Org. Code:</b>	180		25212 WEST ILLINOIS RT 120		
<b>Priority:</b>	5		ROUND LAKE, IL 60073		
<b>Stamp Date:</b>	03-JAN-2013	<b>Brand Name:</b>	20% IV LIPID EMULSION		
<b>PDUFA Date:</b>	03-OCT-2013	<b>Estab. Name:</b>			
<b>Action Goal:</b>		<b>Generic Name:</b>	20% IV LIPID EMULSION		
<b>District Goal:</b>	04-MAY-2013	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; EMULSION, INJECTION; OLIVE OIL; 160GM 001; EMULSION, INJECTION; SOYBEAN OIL; 40GM		
<b>FDA Contacts:</b>	T. MEHTA	Prod Qual Reviewer			3017961712
	D. MILLER	Micro Reviewer	(HFD-003)		3017963854
	C. TRAN-ZWANETZ	Product Quality PM	(HFD-800)		3017963877
	M. KOWBLANSKY	Team Leader			3017961390
<b>Overall Recommendation:</b>	ACCEPTABLE	on 23-SEP-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 07-FEB-2013	by EES_PROD		
	PENDING	on 07-FEB-2013	by EES_PROD		

**Attachment-2:**

**1. Final PI and Labels for Container and Cartons**

(b) (4)



3 Pages Of Draft Labeling Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

## Attachment-3

### POSTMARKETING REQUIREMENTS UNDER 505(o)

Application #(s):	<b>NDA 204508</b>
Communication Type:	Correspondence
Communication Group:	<b>NDA Action</b>
Communication Name:	<b>Approval</b>
Communication ID:	<b>COR-NDAACTION-03</b>
Drafted by:	<b>MBB 9/20/13</b>
Clearance History:	<b>WI: 09/26/13</b> <b>RF:</b> <b>CP/JK:</b> <b>DG:</b>
Finalized:	
Filename:	
Use Statement:	<b>Used to issue an Approval letter to application, effective on date of letter, when acceptable FPL has already been submitted.</b>
Notes:	<b>USE FOR PRESCRIPTION APPROVALS ONLY</b>

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of liver injury in pediatric and neonatal patients, which may be related to the presence of phytosterols, or identify an unexpected serious risk of administration of unfiltered product that contains fragments of the product container.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR-1 Develop and validate an appropriate analytical method for determining the individual component phytosterol content in Clinolipid (lipid injectable emulsion, USP) 20%.

Final Report Submission: MM/YY\*

\*Refer to Approval letter for Final report date

PMR-2 Test the three registration stability batches for the individual component phytosterol content in Clinolipid (lipid injectable emulsion, USP) 20% using the analytical methods developed in PMR ####-1.

Final Report Submission: MM/YY\*

\*Refer to Approval letter for Final report date

PMR-3 Test for the individual component phytosterol content in all batches of Clinolipid (lipid injectable emulsion, USP) 20%, manufactured over a three year period, using the method developed under PMR ####-1. Based on these test results, establish limits for each of the individual component phytosterols in Clinolipid (lipid injectable emulsion, USP) 20% in the product specification.

Final Report Submission: MM/YY\*

\*Refer to Approval letter for Final report date

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

**We remind you of your postmarketing commitments:**

PMC-10 Develop and validate an analytical method for determining cholesterol content in Clinolipid (lipid injectable emulsion, USP) 20%.

Final Report Submission: MM/YY\*

\*Refer to Approval letter for Final report date

PMC-11 Develop and validate an analytical method for determining squalene content in Clinolipid (lipid injectable emulsion, USP) 20%.

Final Report Submission: MM/YY\*

\*Refer to Approval letter for Final report date

PMC-12 Analyze the three registration stability batches for the cholesterol and squalene content, using the analytical methods developed in PMCs #####-10 and #####-11, respectively.

Final Report Submission: MM/YY\*

\*Refer to Approval letter for Final report date

PMC-13 Test all batches of Clinolipid (lipid injectable emulsion, USP) 20% manufactured over a three year period for the cholesterol and squalene content, using analytical methods developed under PMCs #10 and #11, respectively. Based on these test results, establish limits for cholesterol and squalene in the Clinolipid (lipid injectable emulsion, USP) 20% product specification.

Final Report Submission: MM/YY\*

\*Refer to Approval letter for Final report date

Submit chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."

**ADDITIONAL COMMENTS**

We remind you that in your submission dated May 7, 2013, you have committed to file a Prior Approval Supplement to the application to add a comparability protocol for evaluating the effects of changes to the manufacturing process for the Clarity container on extractables from these containers.

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TARUN D MEHTA  
10/02/2013

MOO JHONG RHEE  
10/02/2013  
Chief, Branch IV

# ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

<b>Application:</b> NDA 204508/000 <b>App Date:</b> 03-JAN-2013 <b>Regulation:</b> 03-OCT-2013  <b>Applicant:</b> BAXTER 25212 WEST ILLINOIS RT 120 ROUND LAKE, IL 60073  <b>Priority:</b> 5 <b>Reg. Code:</b> 180	<b>Action Goal:</b>  <b>District Goal:</b> 04-MAY-2013  <b>Brand Name:</b> 20% IV LIPID EMULSION <b>Estab. Name:</b> <b>Generic Name:</b> 20% IV LIPID EMULSION  <b>Product Number; Dosage Form; Ingredient; Strengths</b> 001; EMULSION, INJECTION; SOYBEAN OIL; 40GM 001; EMULSION, INJECTION; OLIVE OIL; 160GM
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**Application Comment:** PRIORITY REVIEW (on 07-FEB-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)

<b>QA Contacts:</b>	T. MEHTA	Prod Qual Reviewer	3017961712
	D. MILLER	Micro Reviewer (HFD-003)	3017963854
	C. TRAN-ZWANETZ	Product Quality PM (HFD-800)	3017963877
	M. KOWBLANSKY	Team Leader	3017961390

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<b>Overall Recommendation:</b>	ACCEPTABLE	on 23-SEP-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 07-FEB-2013	by EES_PROD		
	PENDING	on 07-FEB-2013	by EES_PROD		

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# ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: FEI: 1000359047  
 BAXTER R & D EUROPE SPRL  
 BOULEVARD D'ANGLETERRE 2-4  
 BRAINE L'ALLEUD, , BELGIUM

MF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER  
 FINISHED DOSAGE OTHER TESTER

Establishment Comment: ALTERNATE FOR STABILITY TESTING, DRUG SUBSTANCE TESTING, EXCIPIENT TESTING AND FINISHED PRODUCT TESTING. (on 07-FEB-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)  
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	07-FEB-2013				TRANZWANETZC
SUBMITTED TO DO  NEW SITE	08-FEB-2013	Product Specific and GMP Inspection			SMITHDE
SIGNED INSPECTION TO IB	09-FEB-2013	Product Specific and GMP Inspection			PHILPYE
INSPECTION SCHEDULED	04-APR-2013		21-JUN-2013		PHILPYE
INSPECTION PERFORMED AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, C ONSOLIDATED See EIR	21-JUN-2013		21 JUN 2013	(b) (4)	Michele.PerryWilliams
DISTRICT RECOMMENDATION	27-AUG-2013			ACCEPTABLE INSPECTION	PHILPYE
DISTRICT RECOMMENDATION	29-AUG-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

# ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

**Establishment:** **CFN:** **FEI:** 3002806503

BAXTER SA

BOULEVARD RENE BRANQUART 80  
LESSINES, HAINAUT, BELGIUM

**MF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Establishment Comment:** USED FOR STABILITY TESTING, DS TESTING, EXCIPIENT TESTING, CONTAINER ASSEMBLY, MANUFACTURE OF FINISHED PRODUCT, FINISHED PRODUCT TESTING, FINISHED PRODUCT RELEASE. (on 07-FEB-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)  
EMAIL SENT FOR CLARIFICATION OF PROFILE (on 08-FEB-2013 by D. SMITH (HFD-620) 2402769592)

**Profile:** PROVIDES FOR DS AND EXCIPIENT TESTING, CONTAINER ASSEMBLY, MANUFACTURER OF DP, FINISH PRODUCT TESTING AND RELEASE, AND STABILITY TESTING. (on 31-JAN-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)  
LARGE VOLUME PARENTERALS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	07-FEB-2013				TRANZWANETZC
SUBMITTED TO DO	11-FEB-2013	Product Specific and GMP Inspection			SMITHDE
SITE DOES NOT APPEAR TO HAVE A CDER INSPECTION					
ISSUE INSPECTION TO IB	17-FEB-2013	Product Specific and GMP Inspection			PHILPYE
INSPECTION SCHEDULED	04-APR-2013		18-JUN-2013		PHILPYE
INSPECTION PERFORMED See EIR	18-JUN-2013		18-JUN-2013		Michele.PerryWilliams
DO RECOMMENDATION	27-AUG-2013			ACCEPTABLE INSPECTION	PHILPYE
DO RECOMMENDATION	29-AUG-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

# ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: (b) (4)

MF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: USED FOR HEAVY METALS TESTING (on 18-JAN-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)

Office: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	07-FEB-2013				TRANZWANETZC
SUBMITTED TO DO	08-FEB-2013	GMP Inspection			SMITHDE
SUBSIGNED INSPECTION TO IB	09-FEB-2013	GMP Inspection			PHILPYE
INSPECTION SCHEDULED	16-MAY-2013		<span style="background-color: gray; color: gray;">(b) (4)</span>		IRIVERA
INSPECTION PERFORMED	<span style="background-color: gray; color: gray;">(b) (4)</span>		<span style="background-color: gray; color: gray;">(b) (4)</span>		Karen.Kosar
<p>This inspection of a control laboratory was initiated at the request of CDER and the International Operations Branch under FACTS Assignment #8364803 and PAC's 46832 and 56002. This GMP and Pre-Approval inspection covered NDA 204508, C.P. 7346.832, Pre-Approval Inspections and C.P. 7356.002, Drug Manufacturing Inspections provided guidance. Profile class CTX was covered.</p> <p>The previous FDA inspection, dated <span style="background-color: gray; color: gray;">(b) (4)</span> was a Pre-Approval and GMP inspection covering <span style="background-color: gray; color: gray;">(b) (4)</span>. The inspection was classified as NAI.</p> <p>C. <span style="background-color: gray; color: gray;">(b) (4)</span> continues to operate as a contract control testing laboratory for the testing of raw materials and finished drug products. <span style="background-color: gray; color: gray;">(b) (4)</span></p> <p><span style="background-color: gray; color: gray;">(b) (4)</span></p> <p><span style="background-color: gray; color: gray;">(b) (4)</span> No major deficiencies were revealed during the current inspection. This firm is registered with FDA for 2013.</p> <p>An FDA-483 was not issued. No refusals were encountered. No samples were collected.</p>					
DISTRICT RECOMMENDATION	27-AUG-2013			ACCEPTABLE INSPECTION	PHILPYE
DISTRICT RECOMMENDATION	29-AUG-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

# ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: (b) (4)

MF No: AADA:

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

Establishment Comment: PROVIDES FOR DS MANUFACTURER, PACKAGING, DS TESTING, DS RELEASE, DS STABILITY TESTING, LOCAL  
 (b) (4)

File: DS OLIVE OIL AND SOYBEAN OIL (on 07-FEB-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)  
 (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	07-FEB-2013				TRANZWANETZC
SUBMITTED TO DO  NEW FIRM	08-FEB-2013	Product Specific and GMP Inspection			SMITHDE
ASSIGNED INSPECTION TO IB	09-FEB-2013	Product Specific and GMP Inspection			PHILPYE
INSPECTION SCHEDULED	10-APR-2013		<span style="background-color: gray; display: inline-block; width: 80px; height: 15px;"></span> (b) (4)		IRIVERA
INSPECTION PERFORMED See EIR			<span style="background-color: gray; display: inline-block; width: 300px; height: 15px;"></span> (b) (4)		Michele.PerryWilliams
DO RECOMMENDATION	11-SEP-2013			ACCEPTABLE INSPECTION	PHILPYE
DO RECOMMENDATION	11-SEP-2013			ACCEPTABLE DISTRICT RECOMMENDATION	WITTORFR



**NDA 204508**

**Clinolipid (20% Lipid Injectable Emulsion, USP)**

**Baxter Healthcare Corporation**

**Tarun Mehta**

**Review Chemist**

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

**CMC REVIEW OF NDA 204508  
For the Division of Gastroenterology and Inborn Errors Products  
(HFD-180)**

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## Executive Summary Section

**CMC Review Data Sheet**

1. NDA 204508
2. REVIEW #: 1
3. REVIEW DATE: 18-Jun-2013
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 3, 2013
Amendment 007	May 7, 2013
Amendment 008	May 15, 2013
Amendment 009	May 31, 2013
Amendment 011	June 07, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Baxter Healthcare Corporation.  
Address: 25212 W. Illinois Route 120, Round Lake, IL 60073  
Representative: Kathleen O'Neil  
Telephone: (224) 270 - 4196

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name: Lipid emulsion
- c) Code Name/# (ONDQA only): None
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)  
The RLD is the Intralipid 20% (A 20% Intravenous Fat Emulsion).

10. PHARMACOL. CATEGORY: Total parenteral nutrition

11. DOSAGE FORM: Injection

Executive Summary Section

12. STRENGTH/POTENCY: 20% w/v of essential fatty acids

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

None

Chemical name: Soybean oil and Olive oil

Molecular formula: NA

Molecular Weight: NA

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETE	COMMENTS
25619	II	Baxter	Refined Soybean Oil	1	Adequate	2 – May - 2013	No update since last review Reviewed by Tarun Mehta
25620	II	Baxter	Refined Olive Oil	1	Adequate	2 – May - 2013	No update since last review
(b) (4)	III	(b) (4)	(b) (4)	1	Inadequate	13-June-2013	CDRH consult is requested.  Reviewed by Tarun Mehta
	IV			4	N/A		

<sup>1</sup> Action codes for DMF Table:  
1 – DMF Reviewed.

**Executive Summary Section**

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
- 7 – Other (explain under "Comments")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-499	Intralipid 20% IV fat emulsion

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	6/06/2013	
Microbiology	Recommended for approval	6/11/2013	Dennis Miller
CDRH	IR has been sent	5/02/2013	Jason Toe
EA	Categorical exclusion granted	4/17/2013	Tarun Mehta

## Executive Summary Section

## The CMC Review for NDA 204508

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

The applicant of this NDA has *not* provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has *not* issued an overall “Acceptable” recommendation for the facilities involved in this application.

The label/labeling issues are *not* fully resolved.

Therefore, from the ONDQA perspective, this NDA is not **ready** for approval in its present form per 21 CFR 314.125(b)(1)(6), and (13) until these issues are satisfactorily resolved.

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

1. The applicant agreed to commit to develop a change protocol for the manufacture of container closure to assure extractables from the bag are well controlled if they change manufacturer or raw materials for the bag.
2. The applicant agreed develop appropriate methods to measure 10 phytosterols (plus cholesterol) in manufactured batches, measure the content in all batches manufactured over a 3 year period, and finally use this information to set specifications.

#### II. Summary of CMC Assessments

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

###### (1) Drug Substance

The drug substances used in the proposed drug products are refined oils of soybean and olives. (b) (4)

[REDACTED] The release and stability specifications are based on compendial USP / NF monographs. The DMFs

## Executive Summary Section

were deemed adequate for this NDA. The stability data support the (b) (4) months of retesting period.

**(2) Drug Product**

The drug product is a lipid injectable emulsion USP. The drug product will be marketed in a (b) (4) "Clarity" poly olefin bag. This drug product is already been approved to be used in the countries outside the USA. The proposed drug product is marketed as a source of energy and essential fatty acids. This drug product contains 4:1 ratio of olive oil to soy oil as opposed to RLD and other comparable products, which contain 100% soy oil as a source of lipid.

Sponsor has identified Baxter S.A. Belgium as a drug product manufacturing site. The manufacturing site has been used for manufacturing the drug product approved for European market. The applicant has manufactured (b) (4) of the maximum commercial size batch using the identical manufacturing process and controls. (b) (4)

Clinolipid 20% Lipid Injectable Emulsion, USP, conforms to the USP monograph for Lipid Injectable Emulsion. However, due to the concern over exposure to the high levels of elemental impurities when patients treated with large volume of intravenous parenteral drug product. FDA has requested the applicant to revised the drug product specification using draft ICH Q3D requirements for elemental impurities.

The finished drug product is packaged in a 1000mL (b) (4), dual ported, polyolefin CLARITY (PL 2401-1) container closure system developed and manufactured by Baxter. Each filled container is individually packaged with an oxygen absorber and an oxygen indicator in a clear (b) (4) overpouch, and heat-sealed.

The safety of the CLARITY Container Closure System has been established through a battery of tests including an extractables/leachables characterization and its associated toxicological assessment and successful completion of USP Biological Reactivity and Physicochemical Tests. Detailed discussions are contained in Baxter's DMF (b) (4) CLARITY Container Closure System. The applicant has resolved the concerns of CMC and toxicology groups regarding the extractable and leachable safety.

However, CDRH issues regarding the container closure system still unresolved.

Based on the available data the expiration dating period of 18 months is granted.

## Executive Summary Section

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

The drug product is intended for intravenous infusion only. It is sold in (b) (4) 1000mL container. When infused alone as a support to oral, parenteral or enteral nutrition, Clinolipid 20% can be administered via central or peripheral vein. When administered as a component of parenteral nutrition (with dextrose and amino acids) the central or peripheral venous route should be chosen, depending on the osmolarity of the final infusate.

The following precaution should be taken when this drug product is administered.

Only administration sets and lines that do not contain di-2-ethylhexyl phthalate (DEHP) are recommended for use with lipids. The use of a final filter is recommended during administration of all parenteral nutrition solutions, where possible. Filters of less than 1.2 micron pore size should not be used with lipid emulsions. It is recommended that after opening the bag, the contents should be used immediately, and should not be stored for a subsequent infusion.

**C. Basis for Not-Approval Recommendation**

## 21 CFR 314.125(b)(1)

- The drug product specification needs to be revised according to draft ICH Q3D guidance for elemental impurities in LVP (large volume parenteral).  
The container closure system is not deemed adequate per CDRH consult review.

## 21 CFR 314.125(b)(6)

- The drug product label/labeling are not finalized as of this review.

## 21 CFR 314.125(b)(13)

- The Office of compliance has not issued an overall “Acceptable” recommendation for the facilities involved in this application.

(See the **List of Deficiencies** on p. 66)

## Executive Summary Section

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

*(See appended electronic signature page)*

Tarun Mehta, M.Sc., Branch IV, ONDQA Division II

**B. Endorsement Block:**

*(See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch IV, ONDQA Division II

**C. CC Block:** entered electronically in DFS

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/s/  
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TARUN D MEHTA  
06/20/2013

MOO JHONG RHEE  
06/20/2013  
Chief, Branch IV

## FILING CHECKLIST

<b>NDA Number:</b>	<b>Supplement Number and Type:</b>	<b>Established/Proper Name:</b>
NDA 204-508 (Type 5 application)	original	Lipid Injectable Emulsion (parenteral nutrition)

<b>Applicant:</b>	<b>Letter Date:</b>	<b>Stamp Date:</b>
Baxter Healthcare		01/03/2013

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?	√		
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? <b>This question is not applicable for synthesized API.</b>	√		
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"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		

8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		
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"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		
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.

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

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	√		DMFs referenced Soy oil 25619 Olive oil 25620 Sodium oleate (b) (4) Sodium oleate (b) (4)
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

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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)?	√		By reference to DMF (b) (4)
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?	√		

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.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	√		

*{See appended electronic signature page}*

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

*{See appended electronic signature page}*

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARIE KOWBLANSKY  
03/04/2013

MOO JHONG RHEE  
03/04/2013  
Chief, Branch IV