

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204508Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204508

SUPPL #

HFD #

Trade Name Clinolipid

Generic Name Lipid Injectable Emulsion, USP, 20%

Applicant Name Baxter Healthcare Corporation

Approval Date, If Known PDUFA Date 10/03/13

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18449 Intralipid 20%
NDA# 18969 Liposyn III 20%
NDA# 19531 Nutrilipid 20%

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain: The product has been marketed outside the United States for many years and there are a number of academic clinical studies available which are mostly relevant for safety in adults but also contain efficacy data, however, by themselves not sufficient to make a determination of effectiveness

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

C89 CSW 6/3 08F and C89 CSW 6/3 10F

ATTENTION: We believe that based on the definition below, these studies are technically bioavailability studies; however, given that they assess clinical endpoints, they were listed as clinical investigations.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

same as in 2(c)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO

Title: Regulatory Project Manager and Medical Officer
Date: September 24, 2013

Name of Office/Division Director signing form: Donna Griebel, M.D.
Title: Division Director

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

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

/s/

MATTHEW B BRANCAZIO
10/03/2013

DONNA J GRIEBEL
10/03/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 204508 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Gastroenterology and Inborn Errors PDUFA Goal Date: Oct 3, 2013 Stamp Date: 1/3/2013
Products

Proprietary Name: Clinolipid

Established/Generic Name: Lipid Injectable Emulsion, USP, 20%

Dosage Form: Injectable Emulsion

Applicant/Sponsor: Baxter Healthcare Corporation

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: indicated in adults for parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

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

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.
 Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

⌋ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

neck pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications.

Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

neck subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Action F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

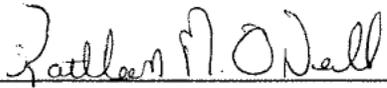
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

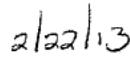
(Revised: 6/2008)

1.3.3 Debarment certification

Baxter Healthcare Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Kathleen O'Neill
Director, Global Regulatory Affairs



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204508 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Clinolipid Established/Proper Name: Lipid Injectable Emulsion, USP, 20% Dosage Form: Lipid Injectable Emulsion		Applicant: Baxter Healthcare Corporation Agent for Applicant (if applicable):
RPM: Matt Brancazio, Pharm.D.		Division: DGIEP
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>NDA 18449 Intralipid 20% (20% IV Fat Emulsion)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>While both products contain soybean oil, the percentage of the olive oil component in Clinolipid comprises roughly 80% of the mixture (20% remaining is soybean oil). Intralipid is 100% soybean oil.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input checked="" type="checkbox"/> This application relies on (explain) both a listed drug and literature.</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 10/3/13</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>October 3, 2013</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 5</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Information Advisory to HHS

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A)(2) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	10/7/13
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval 10/3/13
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	9/25/13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	January 3, 2013
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Intralipid 20% - 06/06 Liposyn III – 09/05

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	n/a
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	n/a
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	10/03/13
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	06/21/13 09/06/13; 06/20/13; 04/26/13
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 02/20/13 <input checked="" type="checkbox"/> DMEPA 07/11/13 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 09/17/13; 08/27/13; <input checked="" type="checkbox"/> SEALD 10/3/13 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	03/04/13
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 05/31/13 <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>PREA was not triggered</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	09/26/13; 09/12/13; 08/27/13; 08/09/13; 06/26/13; 05/17/13; 05/10/13; 05/03/13; 04/30/13; 03/22/13; 03/04/13; 02/13/13; 02/08/13; 01/14/13
❖ Internal memoranda, telecons, etc.	09/23/13; 09/23/13; 03/08/13
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 07/13/11
• EOP2 meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/3/13
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/3/13
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 10/3/13
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	Please refer to CDTL Review
• Clinical review(s) <i>(indicate date for each review)</i>	09/20/13; 03/04/13
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	Please refer to Section 3.3 of the Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None PMHS: 09/10/13; 09/09/13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 02/05/13
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07/26/13; 03/04/13
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 08/08/13; 01/30/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/2/13; 06/20/13; 03/04/13
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 06/11/13; 03/04/13
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None CDRH: 09/26/13 (2); 07/31/13; 06/10/13; 04/22/13
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Please refer to CMC review II B (page 66)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 09/23/13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

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/s/

MATTHEW B BRANCAZIO
10/07/2013

From: [Brancazio, Matthew \(FDA\)](#)
To: [Schwabe, Susan A \(sue_schwabe@baxter.com\)](#)
Cc: [Brancazio, Matthew \(FDA\)](#)
Subject: FW: Baxter "Verify U.S. Spikes performance when interacting with (b) (4) administration Lipid (b) (4) Study Number: 64965
Date: Thursday, September 26, 2013 3:44:02 PM
Importance: High

Sue,

After review of Study 64965 received September 26, 2013, the FDA requests an immediate response to the following:

- 1) You state that all spikes tested meet the acceptance criteria for spike removal. However, review of the test results and information show that P/N 12001029 (b) (4) spike from product ExactaMix Inlet Ref: 174) failed and did not meet the acceptance criteria for spike removal. Provide a detailed rationale and justification as to why you did not consider this to be a failure, and explain why you believe that this met the acceptance criteria.
- 2) You state that the dispensing (b) (4) and direct administration spikes tested meet the acceptance criteria for fall out, leak, and fragmentation as well as spike insertion and removal. However, during the 5 hour fall out test, it was observed that two spikes had a leak immediately after insertion. You state that leak was not an acceptance criteria for that test. Provide a detailed rationale and justification for why the leak failure is considered acceptable.
- 3) You state that the gravity compounding product code 2B8114 (using spike assembly 02-01-07-432) failed the leak requirement as well as the spike insertion. Provide a detailed rationale and justification for why the leak failure is considered acceptable.
- 4) You provided study number 64965 Baxter "Verify U.S. Spikes performance when interacting with (b) (4) administration Lipid (b) (4). Explicitly state what spikes were verified to meet your requirements for the (b) (4) administration site (Twist off protector closure) as represented by the Clarity Lipid (b) (4); (Clinoleic 20%), and what spikes did not meet your requirements.

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

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

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MATTHEW B BRANCAZIO
09/27/2013

MEMORANDUM

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

TELECON MEETING MINUTES

Meeting Date and Time: May 20, 2013 12:00 PM EST
Application Number: NDA 204508
Product Name: Clinolipid
Location: CDER WO 22 ROOM 5270
Indication: **Parenteral nutrition**

Meeting Chair: Rob Fiorentino
Meeting Recorder: Matt Brancazio

FDA Attendees:

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Andrew Mulberg, M.D., Deputy Director, Division of Gastroenterology and Inborn Errors Products
Robert Fiorentino, M.D., M.P.H., Medical Team Leader, Division of Gastroenterology and Inborn Errors Products
Matt Brancazio, Pharm.D., Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products
Dinesh Gautam, Ph.D., Pharmacology Reviewer, Division of Gastroenterology and Inborn Errors Products
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, Division of Gastroenterology and Inborn Errors Products
Tarun Mehta, M.S.c., CMC Reviewer, Office of New Drug Quality Assessment
Marie Kowblansky, Ph.D., CMC Lead, Office of New Drug Quality Assessment
Denise Miller, B.S., Microbiology Reviewer, OPS/New Drug Microbiology Staff
Jason To, B.S., Lead Regulatory Scientific Reviewer, Office of Device Evaluation
Klaus Gottlieb, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products
Jaqueline Ryan, M.D., Combination Products Team Leader, Center for Devices and Radiological Health
Wes Ishihara, Chief, Project Management Staff, Division of Gastroenterology and Inborn Errors Products

External Constituent Attendees (Baxter):

Mary Hise, Clinical
Jan Eilert, CMC
Susan Schwabe, Global Regulatory Lead
Stacey Thompson, Regulatory Pre-CMC

Samantha Turzynski, Regulatory Pre-CMC
Glenn Dennis, Regulatory Pre-CMC
Kathy O'Neill, Global Regulatory

Call-in toll-free number: [REDACTED] (b) (4)

Conference Code: [REDACTED] (b) (4)

1. BACKGROUND:

Baxter Healthcare Corporation submitted NDA 204508 for review by the Division of Gastroenterology and Inborn Errors Products. This review was subsequently granted a priority review and the PDUFA goal date was set to July 3, 2013. This teleconference is to discuss with the sponsor several issues relating to the Product Quality, Microbiology, and Device aspects of the product under review.

2. DISCUSSION:

2.1. Product Quality

1. Extractables/Leachables

FDA expresses concern over an explanation regarding use of a model compound such as pentane versus actual finished product. FDA further expresses concern over the not searching for certain compounds in the study (noted with dashes in the study). FDA further expresses concern with 12 compounds "missing" from the leachables table, but were found in the extractable study. FDA requests an explanation and a measurement of those compounds designated with dashes focused on the CLARITY container for NDA 204508 and the product under review.

2. Process Change Protocol for Clarity Container System

FDA expressed concern with the testing of the bag if Baxter makes a future manufacturing change. FDA suggests a post-marketing commitment describing the testing of the protocol for the bag. Baxter agrees.

3. Status of Phytosterol Testing

FDA expresses concern for the development and validation of a method for testing phytosterols. FDA requests that the finished product be tested due to the variance of the originating materials. FDA suggests testing for a wide array of phytosterols similar to the 2011 study with 12 different phytosterols versus other manufacturers as a blueprint for the finished product. FDA will not commit to the sponsor's request of testing just 3 phytosterols until the array of phytosterols show which phytosterols could be control. Baxter does not think it will be possible before PDUFA date. Baxter is unable to clarify timeline at this point.

2.2. Micro

FDA expresses concern about the lack of data supporting the container closure integrity of the entire 1 liter bag. The studies submitted to date are supportive of the integrity of

the ports only. It is requested that Baxter provide information that supports the integrity of the entire container closure system. This may be in the form of additional integrity studies or manufacturing controls that may be in place that ensures the entire 1 liter bag with ports is integral.

2.3. CDRH/GHDB

FDA expresses concern with ISO 15747 “Plastic Containers for Intravenous Injections,” specifically Annex A “Physical Tests”. The physical tests should be performed and demonstrate that the final finished device is safe and effective when exposed to external conditions during actual use including, but not limited to, temperature, pressure, drops, leakage, etc. It is requested that the sponsor perform these tests per the reference ISO standard.

Discussion: in Europe on holiday today. Annex A information for ingress? Testing and USP testing submitted on 5/15.

Action: timeline 1 week for submission of information or plan/protocol.

3. ACTION ITEMS:

3.1. Baxter

1. Internal discussion regarding information provided
2. Baxter to submit explanation of the use of pentane versus the actual product for extractables and to provide an explanation for the compounds designated with dashes. (1 week timeline)
3. Baxter to provide justification regarding the 3 “control” phytosterols and submit to FDA for review/modification (2 week timeline).
4. Baxter to submit justification of the resealing percentage of the container for FDA review (1 week timeline).
5. Baxter to submit Annex A information and justification for FDA review (1 week timeline).
6. Respond regarding issues raised during teleconference and schedule an additional teleconference to discuss submission strategy.

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/s/

MATTHEW B BRANCAZIO
09/23/2013

MEMORANDUM

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

TELECON MEETING MINUTES

Meeting Date and Time: August 29, 2013 12:00 PM EST
Application Number: NDA 204508
Product Name: Clinolipid
Location: CDER WO 22 ROOM 5270
Indication: **Parenteral nutrition**

Meeting Chair: Rob Fiorentino
Meeting Recorder: Matt Brancazio

FDA Attendees:

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Robert Fiorentino, M.D., M.P.H., Medical Team Leader, Division of Gastroenterology and Inborn Errors Products
Matt Brancazio, Pharm.D., Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products
Quynh Nhu Nguyen, Reviewer, Human Factors, CDRH
Keith Marin, Team Leader, Office of Device Evaluation, CDRH
Jason To, B.S., Lead Regulatory Scientific Reviewer, Office of Device Evaluation, CDRH
Jaqueline Ryan, M.D., Combination Products Team Leader, Center for Devices and Radiological Health
Wes Ishihara, Chief, Project Management Staff, Division of Gastroenterology and Inborn Errors Products

External Constituent Attendees (Baxter):

Dennis Kaucky, Pharm.D., Sr. Mgr. Nutrition – Therapeutic Area Specialty Pharmaceuticals – Medical Products
Eric Nott, Engineering Specialist, Department: R&D
Ann Milliman, Manager II, Global Quality
Gary Zaloga, M.D., MSc Global Medical Director, Nutrition
Mary Hise, Ph.D., RD Director Clinical and Medical Affairs, Nutrition
Kathleen O’Neill, Director, Global Regulatory Affairs
Susan Schwabe, MS Senior Manager, Global Regulatory Affairs

Conference Code: (b) (4)

Call-in toll-free number: (b) (4)

1. BACKGROUND:

This teleconference is a follow-up in reference to the Medeffect e-notice received from Health Canada. This notice explained multiple accounts of TOP dislodgement and fragmentation. FDA requested this teleconference to request additional information on the events.

2. DISCUSSION:

2.1. Clinical

1. You state in your health hazard evaluation SP13-020 “Based on study 759-M-NIV, the estimated defect rate of the membrane being dislodged is 1-2% or a PODME rating of FREQUENT when compounding using the BAXA product code 173.”
 - a. Can you estimate how frequently membrane detachment could occur upon product launch in the United States? Specifically, how many units of the product and what percentage do you think will be subjected to the procedure suspected of being responsible for the membrane detachment?
 - i. Baxter states they are uncertain of the exact number, although they are aware there are more compounding machines in the US than in Canada.
 - ii. Baxter says the complaints is higher with the Exactamix 173 spike and will be recommending the use of qualified spike to their compounding users.
 - iii. FDA expresses concern over the uniqueness of the Exactamix 173 spike. Baxter states the geometry (shoulder and spike length) is the main cause.
 - iv. FDA requests information with regard to other spikes that are interfacing with the Clinoleic product. Baxter states yes, there are, but the compound machine uses the specific spike. FDA requests highlighting of differences between the Exactamix 173 and other administration sets. Baxter clarifies that the Exactamix 173 is ONLY for use in compounding machine, not in patient care sets.
 - v. FDA inquires about administration sets and compounding sets that if they are part of the Baxter testing for interfaces. Baxter states they are planning to test the majority of spikes available.
 - vi. FDA clarifies that there are a combination of factors contributing to the issues we are seeing (mechanical interface, geometrical spike layout, and method of users spiking the device during the process) and asks what

would Baxter recommend to the user for proper spiking process to alleviate the purported problems. Baxter states they could match the recommended technique for that spike. FDA further asks how that is different than the current practice. Baxter clarifies “if a product is longer than others, they could specify that less twisting would be needed.”

- vii. FDA asks if eliminating the twisting motion could eliminate the issue. Baxter states that could be possible solution in addition to other compounding factors.

- b. Could the membrane detachment occur under other circumstances?
2. If membrane dislodgement occurs, how easily can the foreign body be seen in the bag during typical use?
 - a. Baxter states the detectability of the detachment membrane is high due to the color contrast of the foreign body, bag, and color of lipid as well as the size and floatation of the foreign body. Typical infusion line is smaller than the size of the foreign body so it is unlikely that it would go through the line. The material is softer and could fold up and enter the line.
 - b. FDA requests comment from Baxter on smaller, non-visible fragments that could detach and are smaller than the line. Baxter states they have concluded prior studies to detect smaller fragments.
 3. Is it possible that the macroscopically visible membrane fragment can enter the systemic circulation through the customary infusion sets and venous access ports if no in-line filter is being used?
 4. In health centers and hospitals where trained nurses are responsible for IV lipid infusions, how certain are you that an inline filters will be used?
 - a. Baxter states that it is a current ASPEN recommendation, hospitals have protocols outlining the use of TPN administration, etc, but the exact amount is unknown.
 5. In a home health care setting, how frequently do you think inline filters are used/ not used for TPN?
 - a. Baxter states that home users experience a more common practice to use in-line filters because the administration sets are included with the TPN before sent to the patient. Baxter clarifies that the administration set has a filter already attached so there is no further action required by the patient.

6. In your health hazard evaluation you state: “Based on study 1689-RF-ERD it is unlikely that smaller particulate matter will be introduced in the solution.” Can this be investigated more definitively?
7. How many units of product and overall percentage of use do you expect to be used at home?
 - a. Baxter states that the home care use is very low compared to hospital. Baxter states that home care use is (b) (4) units which is approximately (b) (4) of the total lipid market.
8. Please summarize the outstanding study protocols, timelines, etc.
 - a. Baxter states there is a functional study (Study 64965 – included in the previous IR response from Baxter dated: August 20, 2013) 3 weeks from completion evaluating other spikes which will be completed prior to introduction to the United States’ market. This study would provide information to healthcare providers on which spikes to use with the product.
 - b. FDA is requesting information on any planned human factors study. Baxter does not have any human factors studies planned at this time.
9. FDA expresses concern if Baxter has explored the concept of co-packaging their product with an acceptable spike to decrease future issues, how this issue could impact label, and other options.

2.2. CDRH/HF

10. Is dislodgment occurring in both the compounding and infusion ports?
 - a. Baxter states that those two ports are the same and is all the same access.
11. Submit the report for 1689-RF-ERD.
 - a. Baxter will submit this study.
12. Where all the issues reported coming from a pharmacy, home care use, etc?
 - a. Baxter states that all the reports of malfunction were coming from the pharmacy setting. There is a mechanism for home care users to report issues.

3. ACTION ITEMS:

3.1. Baxter

- Highlight the differences (diagram models) between the Exactamix 173 and other administration sets and submit the results.
- Baxter will submit report 1689-RF-ERD to RPM via e-mail and eCTD.
- Submit the results of Study 64965 to be sent to RPM via e-mail and eCTD.

3.2. FDA

- Follow-up internally with regard to requiring a human factors study

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/s/

MATTHEW B BRANCAZIO

09/23/2013



NDA 204508

LABELING PMR/PMC DISCUSSION COMMENTS

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your January 3, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clinolipid (lipid injectable emulsion, USP) 20%.

We also refer to our June 26, 2013, letter in which we notified you of our target date of September 19, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On March 15, 2013, we received your March 15, 2013, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

Matthew Brancazio, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Package Insert

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

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/s/

MATTHEW B BRANCAZIO
09/12/2013



NDA 204508

INFORMATION REQUEST

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) submitted January 3, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clinolipid Lipid Injectable Emulsion, USP, 20%.

We are reviewing the clinical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Using the 14 active-controlled studies with soybean oil-based lipids as a comparator, present adverse reactions (numbers and percentages) by population groups/indications such as elective surgery, trauma surgery, gastrointestinal dysfunction-short-term use, gastrointestinal dysfunction-long-term use, burns, and "other." You may use other categories of your own choosing in order to create sufficiently homogenous TPN user-groups.

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

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
08/27/2013



NDA 204508

INFORMATION REQUEST

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) submitted January 3, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clinolipid Lipid Injectable Emulsion, USP, 20%.

We also refer to your August 9, 2013, submission, containing information related to a recently issued MedEffect e-notice from Health Canada noting the potential for the presence of particles from the administration port material of Clinoleic 20%. Your submission stated that Baxter is currently designing a study to duplicate the Twist Off Protector (TOP) membrane separation.

In reviewing your August 9, 2013, submission, we have the following additional information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the study protocol and timeline for completion for the TOP membrane separation study.
2. Submit the complaints and narratives that initiated the MedEffect e-notice.
3. Provide the names of other products currently using the Clarity container system both within the United States and internationally as well as any similar complaints and/or errors associated with the TOP membrane separation.
4. Provide any usability testing performed on the Clarity container and the results of that usability testing.
5. A reference is made to a medical risk assessment which concluded that the generation of particulate matter upon spiking of the Clarity container was low. Provide this medical risk assessment.

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

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
08/09/2013



NDA 204508

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Baxter Healthcare Corporation
Attention: Kathleen O’Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O’Neill:

Please refer to your January 3, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ClinOleic 20% Lipid Injectable Emulsion, USP.

On June 7, 2013, we received your June 7, 2013, solicited major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 3, 2013.

We also note that we are awaiting your final submission in response to our April 30, 2013, Information Request. This request, for Annex A.3 of ISO 15747, is a critical portion of the review and was clarified during the May 20, 2013, teleconference between Baxter Healthcare Corporation and the Division of Gastroenterology and Inborn Errors Products.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 19, 2013.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

BRIAN K STRONGIN
06/26/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204508

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Baxter Healthcare Corporation
25212 W. Illinois Route 120
Round Lake, IL 60073

ATTENTION: Kathleen O'Neill
Director, Global Regulatory Affairs

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) dated January 2, 2013, received January 3, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lipid Injectable Emulsion, USP, 20%.

We also refer to your March 25, 2013, correspondence, received March 26, 2013, requesting review of your proposed proprietary name, Clinolipid. Please also refer to your April 26, 2013, amendment to that request. We have completed our review of the proposed proprietary name, Clinolipid, and have concluded that it is acceptable.

The proposed proprietary name, Clinolipid, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 26, 2013, and April 26, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew Brancazio at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/21/2013



NDA 204508

INFORMATION REQUEST

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) submitted January 3, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clinolipid Lipid Injectable Emulsion, USP, 20%.

We are reviewing the clinical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. You previously stated: “Baxter is not aware of Essential Fatty Acid Disease (EFAD) occurring in patients receiving either ClinOleic or Intralipid as part of their parenteral nutrition regimen (i.e., no Adverse Events (AEs) of EFAD have been reported to Baxter or published in the medical literature). Cases of EFAD that have been reported in the literature result from the administration of lipid-free parenteral nutrition. However, it is clear that an inadequate supply of Essential Fatty Acid (EFA) can lead to EFAD in patients receiving parenteral nutrition.¹”

FDA has identified a case report where Essential Fatty Acid Disease (EFAD) developed within 2 weeks in an adult postsurgical patient who received a reduced amount of lipids because of hypertriglyceridemia. In particular, we note that the product used appears to have had twice the linoleic acid concentration of Clinolipid².

This seems to suggest that under certain clinical scenarios, it is possible that EFAD may occur when Clinolipid is the sole source of lipids, especially when the EFA requirements are high (such as in preterm infants) and the daily dose is reduced.

Please provide your perspective on this case report and provide a list of other clinical scenarios in which patients receiving Clinolipid may be at a higher risk EFAD.

¹ 2.7.3 Summary of Clinical Efficacy. ClinOleic 20% Lipid Injectable Emulsion, USP Page 123 of 158

² Roongpisuthipong, Wanjarus, et al. "Essential fatty acid deficiency while a patient receiving fat regimen total parenteral nutrition." *BMJ Case Reports* 2012 (2012).

³ 2.7.3 Summary of Clinical Efficacy. ClinOleic 20% Lipid Injectable Emulsion, USP Page 128 of 158. Table 16.

2. We acknowledge your calculation of the Holman index for the three submitted pediatric studies³; however, we note that:
 - a. Study C 88 CSW 6/3 03 F had a treatment duration of 17 ± 5 days and a total of 18 patients. The primary and secondary endpoints are not stated and the evaluation of EFA was not stated as a goal. The statistical analysis plan lacks a sample size calculation.
 - b. Study CT 2402/P14/93/F had a mean duration of 56 days. The sample size does appear to have been adequately justified. In addition, evaluation of EFA was not pre-specified as an objective and the lipid dose was individually adjusted at the discretion of the provider.
 - c. Study CT 2402/P15/94/G was conducted in premature infants (28 to 36 weeks). The duration of treatment was only 7 days.

It does not appear that the above studies, by themselves, exclude a risk of EFAD with Clinolipid. We are especially concerned about the absence of adequate long-term data in the population of premature infants. We also note that in the short-term study CT 2402/P15/94/G, the Holman index (group average) associated with Clinolipid was 5 times higher at the end of the 7-day period than the one associated with Intralipid. Although we acknowledge that this was below the cutoff for EFAD, this change occurred within 7 days and potentially could have continued to increase if follow-up had been longer. We further note that your data are calculated ratios of reported means. This approach could easily obscure the occurrence of EFA in isolated patients.

Please provide comments on these observations and whether there is existing longer term data that suggests this is not a clinical concern.

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

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

¹ 2.7.3 Summary of Clinical Efficacy. ClinOleic 20% Lipid Injectable Emulsion, USP Page 123 of 158

² Roongpisuthipong, Wanjarus, et al. "Essential fatty acid deficiency while a patient receiving fat regimen total parenteral nutrition." *BMJ Case Reports* 2012 (2012).

³ 2.7.3 Summary of Clinical Efficacy. ClinOleic 20% Lipid Injectable Emulsion, USP Page 128 of 158. Table 16.

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/s/

RICHARD W ISHIHARA
05/17/2013



NDA 204508

INFORMATION REQUEST

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) submitted January 3, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clinolipid Lipid Injectable Emulsion.

We are reviewing the clinical sections of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Summarize the results of the studies that measured immune function, lipid peroxidation, or any measure relevant to nutritional immunology comparing Clinolipid with a soybean oil-based lipid comparator both in the Baxter studies contained in this NDA and in the published literature.
 - a. **Present the data in tables that show individual results of these studies organized by age groups and analysis type or parameter. For example, TBARS followed by a discussion and conclusion.**
 - b. **Organize the table in manner that allows for comparison of the data between Clinolipid and comparators.**

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

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
05/10/2013



NDA 204508

INFORMATION REQUEST

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) submitted January 3, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ClinOleic 20% Lipid Injectable Emulsion, USP.

We are reviewing the chemistry, manufacturing, and control (CMC) section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Add testing and limits for phytosterol content to the drug product specification.

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

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
05/03/2013



NDA 204508

INFORMATION REQUEST

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) submitted January 3, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clinolipid Lipid Injectable Emulsion, USP, 20%.

We are reviewing the d sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a detailed rationale and justification as to why you chose to test only according to USP monograph <381>: penetrability, fragmentation, and self-sealing capacity.
2. Provide the test reports of the following functional tests per USP monograph <381>: penetrability, fragmentation, and self-sealing capacity. Ensure that your response outlines the procedures, conditions, and parameters in which the device was subjected to, and explain how this testing demonstrates the final, finished device's resistance to external exposures during actual use including, but not limited to, temperature, pressure/altitude, humidity, drops, leakage, penetrability, self-sealing, etc.

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

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
04/30/2013



NDA 204508

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Baxter Healthcare Corporation
25212 W. Illinois Route 120
Round Lake, IL 60073

ATTENTION: Kathleen O'Neill
Director, Global Regulatory Affairs

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) dated and received January 3, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lipid Injectable Emulsion, USP, 20%.

We acknowledge receipt of your March 25, 2013, correspondence, on March 26, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of March 26, 2013.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Phong Do, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301)796-4795. For any other information regarding this application, contact Matthew Brancazio, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

FRANKLIN T STEPHENSON
04/25/2013

CAROL A HOLQUIST
04/26/2013



NDA 204508

GENERAL ADVICE

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director- Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ClinOleic 20% Lipid Injection Emulsion, USP

We also refer to your January 3, 2013, submission, containing a new drug application.

We contacted you on Wednesday, March 13, 2013, requesting a t-con to discuss your leachable and extractable data in DMF (b) (4) specifically your pentane extraction studies, Tables E1 and E2.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Marie Kowblansky, Ph.D.
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosed: Meeting minutes from the t-con

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: March 18, 2013 12:00 PM-12:30 PM

Application Number: NDA 204508

FDA ATTENDEES:

Office of New Drug Quality Assessment

Marie Kowblansky, Ph.D., CMC Lead

Tarun Mehta, Ph.D., ONDQA Reviewer

Cathy Tran-Zwanetz, Regulatory Project Manager

Office of New Drug- Division of Gastroenterology and Inborn Errors Products

Matthew Brancazio, PharmD

SPONSOR ATTENDEES:

Jerry Gass, Research and Development

Denis Jenke, Research and Development

Stacey Thompson, Global Regulatory Affairs

Glenn Dennis, Global Regulatory Affairs

Susan Schwabe, Global Regulatory Affairs

1.0 BACKGROUND

FDA requested this meeting to discuss information that would need to be clarified or submitted to the NDA application or to the the applicant's DMF (b) (4)

2. DISCUSSION

The following issues were discussed:

1. The meaning of the dashes in Table E2 regarding leachables from the (b) (4) bag would need to be defined. Do these dashes mean that the testing did not include testing for the particular compounds designated by the dashes or that they were not detected in the test? If they were not detected, the limit of detection needs to be stated.

2. The application states that pentane has been used as a nonpolar solvent for extraction studies from the (b) (4) bag, but FDA could not find the extraction study data in the application. The applicant was requested to submit this data or provide detailed information regarding the location of this information in the submission. FDA further stated that the pentane extractables fingerprint may be a suitable approach for qualifying any future manufacturing changes that may be made to the bag or its components; a two year leachables study would not be practical for this purpose. After some discussion FDA recommended that a comparability protocol be submitted to deal with changes to the manufacturing process for the bag. Although the applicant suggested that a comparability protocol was not required because such changes would be reported in supplements, FDA

indicated that since there are no specifications for the bag, a comparability protocol would be the best way to ensure that the (b) (4) bags were appropriately evaluated when manufacturing changes occur. However, FDA would be willing to discuss any alternate approaches that may be proposed by the applicant.

3. A statement should be provided that the (b) (4) bag conforms to the appropriate CFR requirements for food contact materials

4. The product will need specification limits for elemental impurities. During the meeting, FDA indicated that conformance to either the newly publish USP monograph <232> or the forthcoming ICH limits would be acceptable. However, as a result of post-meeting discussions of this topic at FDA, we are revising our advice to you regarding this matter: 1) Your product will need to conform to the requirements listed in Table 1 of USP <232> , including the last column in that Table which limits the elemental impurities in terms of Component Limits (μ /g) and 2) you will need to test for elemental impurities in each batch of product, with limits being defined on the basis of permitted daily exposure (PDE) for parenteral product, as defined in Table 1 of USP <232>, and based on the maximum administered dose for your product. The elements that need to be tested are (b) (4) other (b) (4) that may be used in your manufacturing process.

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/s/

CATHERINE A TRAN-ZWANETZ
03/22/2013

MARIE KOWBLANSKY
03/22/2013

MEMORANDUM

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

MEETING DATE: March 7, 2013
TIME: 3:30 PM
LOCATION: WO 22 Room 5440
APPLICATION: NDA 204508
DRUG NAME: (b) (4) (lipid injectable emulsion USP)
TYPE OF MEETING: Proposed Proprietary Name

MEETING CHAIR: Denise Baugh

MEETING RECORDER: Phong Do

FDA ATTENDEES:

Lubna Merchant, Pharm.D., M.S., Team Leader, DMEPA
Denise Baugh, Pharm.D., Safety Evaluator, DMEPA
Phong Do, Pharm.D., SRPM
Tarun Mehta, CMC reviewer, DNDQA2

EXTERNAL CONSTITUENT ATTENDEES:

Mary Hise, Global Medical Affairs, Nutrition
Julie Retzinger, Regulatory, Global Strategic Labeling
Christine Synder, Global Marketing
Amy Giertych, Global Regulatory Affairs
Kathy O'Neill, Global Regulatory Affairs
Sue Schwabe, Global Regulatory Affairs

(b) (4)

Background

Baxter Healthcare Corporation (Baxter) submitted the proposed primary proprietary name, (b) (4) for NDA 204508 on January 24, 2013.

DMEPA requested this teleconference to inform Baxter of preliminary concerns identified during the review of the proposed proprietary name, (b) (4).

Product Information

- Active Ingredient: lipid injectable emulsion, USP, 20%
- Indication of Use: for parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated.
- Route of Administration: intravenous infusion
- Dosage Form: injectable emulsion
- Strength: 20%
- Dose and Frequency: dose depends upon energy expenditure, clinical status, body weight, tolerance, ability to metabolize and consideration of additional energy given to the patient; recommended dosing is as follows:

Population	Usual Daily Lipid dosage (g/k/day)
Adults	1 to 1.5 (not to exceed 2.5)
(b) (4)	

- How Supplied: 1000 mL; 1000 mL/bag in a ‘6 pack’
- Storage: : 20°C to 25°C (68°F to 77°F)
- Container and Closure System: (b) (4), dual ported 1000 mL (b) (4) polyolefin bag. A (b) (4) clear overpouch (secondary packaging) provides protection from oxygen ingress and water loss during long term storage of the drug product

Meeting Objectives

This is a courtesy call to notify Baxter Healthcare Corporation of DMEPA’s preliminary findings and safety concerns with regards to the proposed proprietary name, (b) (4), submitted January 24, 2013.

Discussion

DMEPA’s preliminary review has identified that the proposed proprietary name, (b) (4)

Therefore, this proprietary name is not in accordance with (b) (4)

Therefore, DMEPA finds the proprietary name, (b) (4) unacceptable.

Regulatory Options

1. Wait for DMEPA to complete the review of [REDACTED]^{(b) (4)} by the OSE PDUFA goal date of April 24, 2013 and issue a formal decision (most likely a denial of the name).
2. Withdraw the proposed name, [REDACTED]^{(b) (4)}, and submit another name for review.

The sponsor decided to discuss their options internally and will respond to the FDA with their decision by March 14, 2013.

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/s/

PHONG DO
03/08/2013



NDA 204508

FILING COMMUNICATION

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director, Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) dated January 3, 2013, received January 3, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for ClinOleic 20% Lipid Injectable Emulsion, USP.

We also refer to your amendments dated January 24, February 11, and February 22, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is July 3, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 12, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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

Highlights (HL):

1. White space must be present before each major heading in HL. White space was omitted between Drug Interactions heading and Use in Specified Populations heading.
2. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet). Include the reference section for the summarized statement in the Adverse Reactions section of HL.
3. The date identified under the Initial U.S. Approval in HL must refer to the four-digit year in which FDA initially approved a new molecular entity. The date identified should be 1975.
4. For the Boxed Warning, all text must be **bolded**.

Contents: Table of Contents (TOC)

5. The title for the Boxed Warning must be **bolded**. The box around the title may be removed.
6. All section headings must be **bolded** and in UPPER CASE. “WARNINGS and PRECAUTIONS” should be “WARNINGS AND PRECAUTIONS”.
7. All subsection headings must be indented.

Full Prescribing Information:

8. For the Boxed Warning, all text must be **bolded**.

We request that you resubmit labeling that addresses these issues by March 15, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

DONNA J GRIEBEL
03/04/2013



NDA 204508

INFORMATION REQUEST

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) submitted January 3, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ClinOleic 20% Lipid Injectable Emulsion, USP.

We are reviewing the regulatory, chemistry, manufacturing, and control, and non-clinical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Non-Clinical
 - a. [REDACTED] ^{(b) (4)} was identified as one of the leachables under simulated use condition of your product. No safety information for this leachable was provided in the NDA submission. Please provide a nonclinical safety assessment of [REDACTED] ^{(b) (4)} based on its potential genotoxicity and general toxicity following repeated administration of the compound.
2. Chemistry, Manufacturing, and Control
 - a. Please submit three hard copies of the Methods Validation packages.
3. Regulatory
 - a. Per FD&C Act 306(k)(1), any application for approval of a drug product shall include a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306(a) or (b)] in connection with such application. Submit the debarment certification for your application.
 - b. Submit financial disclosure forms FDA 3454 and/or 3455 with authorized signature per 21 CFR 54.4(a)(1) and (3), as appropriate.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

BRIAN K STRONGIN
02/08/2013



NDA 204508

INFORMATION REQUEST

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

Please refer to your New Drug Application (NDA) submitted January 3, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ClinOleic 20% Lipid Injectable Emulsion, USP.

We have the following comments and information requests.

1. Provide four samples of ClinOleic 20% to assist us in the review of the application from a medication errors perspective. Based upon our post marketing experience, medication errors can occur as a result of misinterpretation of the name as well as during the patient's/healthcare provider's interaction with the actual product. Therefore, we would like a sample that represents in every way what Baxter Healthcare Corporation intends to introduce into the marketplace (e.g., with the proposed name and all other proposed information affixed to the bag).

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

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
02/13/2013



NDA 20458

NDA ACKNOWLEDGMENT

Baxter Healthcare Corporation
Attention: Kathleen O'Neill
Director – Global Regulatory Affairs
25212 W. Illinois Route 120
Round Lake, Illinois 60073

Dear Ms. O'Neill:

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

Name of Drug Product: ClinOleic 20% (20% Lipid Injectable Emulsion, USP)

Date of Application: January 3, 2012

Date of Receipt: January 3, 2012

Our Reference Number: NDA 204508

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 4, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me, Regulatory Project Manager, at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

LCDR Matt Brancazio, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MATTHEW B BRANCAZIO
01/14/2013



PIND 74,881

MEETING MINUTES

Baxter Healthcare Corporation
Attention: Susan Schwabe
Global Regulatory Affairs
1620 Waukegan Road
McGaw Park, Illinois 60085

Dear Ms. Schwabe:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ClinOleic 20% Intravenous Lipid Emulsion.

We also refer to the meeting between representatives of your firm and the FDA on July 13, 2011. The purpose of the meeting was to obtain agreement with the Agency on the requirements to support registration of ClinOleic 20% Intravenous Lipid Emulsion (ClinOleic) in the United States (US).

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

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

Sincerely,

{See appended electronic signature page}

Frances Fahnbulleh, PharmD
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- 1) Meeting Minutes
- 2) Sponsor Slide Presentation



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: July 13, 2011
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1417

Application Number: PIND 74, 881
Product Name: ClinOleic 20% Intravenous Lipid Emulsion.

Indication: ClinOleic is indicated for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Sponsor/Applicant Name: Baxter Healthcare Corporation

Meeting Chair: Robert Fiorentino, M.D., M.P.H., Medical Team Leader

Meeting Recorder: Frances Fahnbulleh, Pharm.D, Regulatory Project Manager

FDA ATTENDEES

Andrew Mulberg, M.D., FAAP, CPI, Deputy Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joyce Korvick, M.D., Deputy Director of Safety, DGIEP
Robert Fiorentino, M.D., MPH, Medical Team Leader, DGIEP
Helen Sile, M.D., Medical Reviewer, DGIEP
Dinesh Gautam, PhD., Pharm/tox Reviewer, DGIEP
Sushanta Chakder, PhD., Pharm/tox Supervisor, DGIEP
Marie Kowblansky, PhD., CMC Lead, Office of New Drug Quality Assessment
Maria Walsh, RN, MS, Associate Director for Regulatory Affairs, Office of Drug Evaluation III
Frances Fahnbulleh, PharmD, Regulatory Health Project Manager, DGIEP

Hari Sachs, M.D., Medical Team Leader, Pediatric and Maternal Health Staff
(PMHS)

Laurie Conklin, M.D., Medical Reviewer, PMHS

Jouhayna Saliba, PharmD, Sr. Regulatory Program Manager, CDER Drug Shortage
Program

George Greeley, Project Manager, PMHS

Sue Chih Lee, PhD, Team Leader, Office of Clinical Pharmacology

SPONSOR ATTENDEES

Susan Schwabe, MS Senior Manager, Global Regulatory Affairs

Amy Giertych Senior Director, Global Regulatory Affairs

Mary Hise, PhD, RD Director Clinical and Medical Affairs, Nutrition

Gary Zaloga, MD, MSc Global Medical Director, Nutrition

Fouad Amer, MD, MPH Senior Medical Director, Nutrition

Jerome Gass, DVM, DA, CVP, DABT, Principal Scientist, Pathobiology

William Zhao, PhD, Director, Biostatistics, Medical Products

1.0 BACKGROUND

Baxter is requesting a Type B meeting to discuss a potential alternative lipid emulsion that would address the current shortage situation. The product is registered in numerous countries outside of the US (most European countries, Canada, Australia, China and other countries worldwide).

Additionally, two investigator- initiated INDs have been opened in the US.

ClinOleic is comprised of a mixture of refined olive oil and refined soybean oil in an approximate ratio of 4:1 (Olive: Soy). ClinOleic is indicated for Parenteral Nutrition when oral or enteral nutrition is not possible, insufficient or contraindicated. As a lipid emulsion, ClinOleic provides a source of calories and essential fatty acids for patients requiring parenteral nutrition. It was developed to provide an IV lipid emulsion having a lower proportion of polyunsaturated fatty acids while still providing an adequate amount of essential fatty acids (EFA) to prevent EFA deficiency in adult and pediatric patients requiring parenteral nutrition.

MEETING OBJECTIVES

The purpose of the meeting is to obtain agreement from the Agency on the requirements to support registration of the lipid product in the US.

The meeting objectives are to: 1) Introduce ClinOleic 20% IV lipid emulsion to the Agency 2) Obtain agreement from the Agency that nonclinical and clinical data generated to date will support registration of ClinOleic 3) Obtain agreement from the Agency that pediatric clinical data will support an indication in the pediatric population.

2. DISCUSSION

Question #1: Nonclinical

Baxter has conducted a series of nonclinical studies that characterize the safety profile of ClinOleic. These studies have supported the marketing authorizations in the European Union (EU), Canada, Australia, China, and numerous other countries worldwide. These studies include single- and repeat-dose toxicity studies and pharmacokinetic and pharmacodynamic studies in multiple species, including rat and dog. A summary of the nonclinical data that will be included in the ClinOleic NDA is provided in Attachment 2 – Section 2.4 Nonclinical Overview.

It is Baxter's position that the nonclinical studies that evaluated ClinOleic support the clinical safety of the product for the intended patient population and are adequate to support product registration for the proposed indication.

Does the Agency concur?

FDA Response to Question #1:

Nonclinical studies conducted with ClinOleic appear to support the safety of the product for the intended patient population. However, we will need to review the full study reports to assess the nonclinical safety of the product.

Discussion: The sponsor accepted FDA's response, no discussion occurred

Question #1a: Clinical

Baxter intends to submit the following body of clinical data in a 505(b)(1) NDA for ClinOleic for the proposed indication and intended patient populations:

- Data from 15 ClinOleic clinical trials and 3 additional clinical trials that evaluated triple-chamber combination products (OliClinomel and Olimel) containing the ClinOleic emulsion in adults demonstrating the lipid emulsion provides a source of calories and essential fatty acids for patients requiring parenteral nutrition.
- Clinical efficacy and safety data from 3 ClinOleic trials and 1 additional trial that evaluated a triple-chamber combination product (Numeta) containing the ClinOleic emulsion conducted in a pediatric population.
- A cumulative summary of Periodic Safety Update Reports for the ClinOleic product in the EU and rest of world that covers 15 years of market experience.
- A cumulative summary of supporting data from completed and ongoing investigator-initiated trials evaluating the ClinOleic emulsion in the US.
- A cumulative summary of scientific journal articles evaluating adult and pediatric patients exposed to ClinOleic and published over the period of 1992 through 2010.

a. Baxter proposes that the body of clinical data described in Attachment 3 – Section 2.7.3, Summary of Clinical Efficacy; Attachment 5 – Review of Published Literature; and Attachment 6 – Summary of US Investigator-Initiated Trials, is sufficient to demonstrate the safety and efficacy of ClinOleic as a source of calories and essential fatty acids for patients requiring parenteral nutrition.

Does the Agency concur?

FDA Response to Question #1a:

FDA is currently engaging in internal discussions regarding the most appropriate regulatory strategy for your product. We are unable to provide definitive agreements at

this time but look forward to discussing issues pertinent to the development of your product.

It is possible that the data you have collected to date could demonstrate the safety and efficacy of ClinOleic as a source of calories and essential fatty acids.

It is not clear if an adequate and well-controlled clinical trial has been performed with ClinOleic that can demonstrate effectiveness or a clinically meaningful benefit, or whether such trials are feasible. Further discussion both internally and with Baxter will be needed to help us identify the most suitable approach.

It is possible that a 505(b)(2) application that relies on the Agency's previous findings of safety and/or effectiveness for a listed drug (e.g., IntraLipid) could be submitted (see our response to Question 3 below). However, you would also need to provide evidence that ClinOleic can provide adequate essential fatty acids to patients receiving longer term parenteral nutrition. In addition, you will need to submit justification, with supportive data, that the lipid composition and emulsion formulation of ClinOleic would not pose new safety concerns over currently available IV lipid emulsions. At this time, it is not clear if the data you have collected to date will be sufficient for this purpose or if additional studies (e.g., PK/PD) are warranted.

Please clarify in what format this data will be submitted under the NDA, including whether detailed clinical study reports will be available and how you plan on presenting an Integrated Summary of Efficacy across multiple trials. The adequacy of the data to support efficacy and safety would be a review issue.

Discussion during meeting:

Sponsor discussed clinical studies that they believe could address the agency's concerns regarding the possibility of EFA deficiency. They also clarified that they intend to submit full study reports in the NDA and will have datasets available. Sponsor proposed to submit to the FDA their plan for the ISE, including the methods by which comparisons will be made across trials. FDA noted that the blinded Randomized Controlled Trials might be more relevant in demonstrating efficacy and considers the open label trials as supportive. FDA agreed to work with the sponsor on planning a future meeting to discuss their plan as well as issues discussed under Question #3.

Question #1b:

ClinOleic was first approved in France in 1995 and units sold to date correlate to an estimated patient exposure of over 1 million patients. Additionally, OliClinomel, a triple-chamber

combination product containing the ClinOleic emulsion approved in 2001, has had over (b) (4) units sold internationally since that date, correlating to an estimated patient exposure of approximately 3.9 million patients.

b. Baxter proposes that the patient population exposure from the studies listed in Attachment 2 – Section 2.4 Nonclinical Overview and Attachment 4 – Section 2.7.4, Summary of Clinical Safety, along with the years of market experience, is sufficient to establish the clinical safety of ClinOleic for the proposed indication in the intended patient populations.

Does the Agency concur?

FDA Response to Question #1b:

See our response to Question 1a.

The clinical safety data described might be considered supportive, however this will be a review issue. We encourage you to discuss what post-marketing analyses have been or could be performed that might support the clinical safety of ClinOleic.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question #1c:

ClinOleic was evaluated in 3 clinical trials in children ranging in age from preterm neonates to 9 years. An additional trial with a triple-chamber combination product (Numeta) containing the ClinOleic emulsion was conducted in pediatric patients ranging in age from preterm neonates to 17 years. The results of these trials demonstrated that ClinOleic provided an adequate supply of lipids for the proposed indication. Additionally, 7 published clinical trials in pediatrics evaluated the efficacy and safety of ClinOleic and are summarized in Attachment 5 – Review of Published Literature.

c. Baxter proposes that these studies satisfy the requirements of the Pediatric Rule.

Does the Agency concur?

FDA Response to Question #1c:

This NDA would trigger PREA, as the product contains a new formulation. Whether or not the submitted studies fulfill PREA will be a review issue. It is possible that additional clinical studies in pediatric patients may be required.

Clarification:

Since ClinOleic is not considered a new active ingredient, new dosage form, new route of administration, new indication, or new dosing regimen, further pediatric studies are not required under PREA. *This was communicated to the sponsor after the preliminary responses were sent, but prior to the meeting. However, the Agency encourages further studies demonstrating long and short-term safety and efficacy in children and infants.*

Question #2: Chemistry, Manufacturing, and Controls

Baxter seeks to offer the ClinOleic product in volumes of (b) (4) 1000 mL. The same emulsion and volumes have been marketed in Europe for 15 years. Stability data for the European product demonstrate that the lipid emulsion is stable under long-term storage conditions. A summary of the chemistry and manufacturing information the ClinOleic product is provided in Attachment 7 - Chemistry, Manufacturing and Controls.

Additionally, NDA registration stability studies will be conducted in accordance with ICH guidance for conduct of stability studies. Baxter proposes to bracket volumes by placing 3 batches each of the smallest (b) (4) and largest (1000 mL) volume products on stability. Baxter plans to submit the application with 6 months accelerated data and 6 months real time data at the time of filing, requesting an 18 month expiry. Stability data from subsequent data points will be provided during the review of the application as results become available.

Does the Agency concur with Baxter's proposed bracketing and approach for the stability registration studies?

FDA Response to Question #2:

Your proposed bracketing approach is acceptable, but you should be aware that an 18-month expiry will not be possible based on the submission of only six months of real time stability data unless the data are updated with an additional three months of data while the application is under review. However, please note that updated data will need to be received no later than five months into the review clock. Any data received beyond that time will not be considered for the purpose of expiration dating.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question #3: Registration Approach

Baxter intends to submit an NDA for ClinOleic under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. Baxter requests concurrence from the Agency that the existing data will support the indication and registration of the product and sufficient to support the safety and efficacy of the ClinOleic product.

Does the Agency concur with Baxter's proposed registration approach?

FDA Response to Question #3:

A 505(b)(1) approach would be possible, however as an alternative, you may consider pursuing a 505(b)(2) regulatory pathway by relying on the Agency's previous findings of safety and effectiveness for a listed drug (e.g., IntraLipid). We look forward to discussing this option further.

We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Discussion:

FDA stated that they are still discussing whether additional data would be needed to adequately support safety and efficacy to enable registration of ClinOleic.. The FDA seeks time to evaluate whether additional studies or analyses prior to submitting the NDA would be advisable or recommended. FDA would be unable to provide any conclusions about the adequacy of the studies collected to date to support efficacy and safety until they are formally submitted under an NDA.

Sponsor requested clarification about the 505(b)(2) regulatory pathway but acknowledged that bridging their product to a reference approved product in the US would be challenging. FDA will need to discuss internally whether the 505(b)(2) pathway is a feasible option..

FDA agreed to meet with the sponsor to discuss this issue further after both the FDA and sponsor have had time to discuss internally. Sponsor asked if they could check-in with the FDA to determine the status of the internal discussions and the FDA agreed to that plan. Baxter appreciates all feedback from the agency and looks forward to future deliberations following internal consults and discussion surrounding intravenous nutritional product development within the agency.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

4.0 ACTION ITEMS

There were no action items

5.0 ATTACHMENTS AND HANDOUTS

Sponsor slide presentation attached

8 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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/s/

FRANCES G FAHNBULLEH
08/26/2011