

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204508Orig1s000

OTHER REVIEW(S)

[COMBINED] PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 204508
Product Name: CLINOLIPID

PMR/PMC Description: Develop and validate an appropriate analytical method for measuring phytosterol levels in plasma.

PMR/PMC Schedule Milestones: Final Protocol Submission: n/a
Study/Trial Completion: n/a
Final Report Submission: 12/31/2014
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This analytical method for phytosterols is required to allow for completing the separate PMR to evaluate an unexpected serious risk of liver injury in pediatric and neonatal patients, which may be related to the presence of phytosterols.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This analytical method for phytosterols is required to allow for completing the separate PMR to evaluate an unexpected serious risk of liver injury in pediatric and neonatal patients, which may be related to the presence of phytosterols.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Develop and validate an appropriate analytical method for measuring phytosterol levels in plasma.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

Develop and validate an appropriate analytical method for measuring phytosterol levels in plasma.

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 204508
Product Name: CLINOLIPID

PMR/PMC Description: Conduct a human factors study to assess user comprehension of the label's instructions to use an inline filter with pore size of 1.2 microns during administration of Clinolipid (lipid injectable emulsion, USP) 20% or an admixture containing Clinolipid (lipid injectable emulsion, USP) 20%. In addition, the study should evaluate the ability of the user to appropriately spike the product's administration port. The study should enroll representative user populations, including pharmacists, nurses, and home health care nurses.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/2014</u>
	Study/Trial Completion:	<u>04/2014</u>
	Final Report Submission:	<u>06/2014</u>
	Other:	<u>MM/DD/YYYY</u>

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Post marketing reports from other countries indicate the potential of pieces of administration port from bag to dislodge during spiking. This study needs to evaluate this potential in real-world settings and users.

7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Post marketing reports from other countries indicate the potential of pieces of administration port from bag to dislodge during spiking. This study needs to evaluate this potential in real-world settings and users. We require a human factors study to assess user comprehension of the label's instructions to use an inline filter with pore size of 1.2 microns during administration of Clinolipid (lipid injectable emulsion, USP) 20% or an admixture containing Clinolipid (lipid injectable emulsion, USP) 20%. In addition, the study should evaluate the ability of the user to appropriately spike the product's administration port. The study should enroll representative user populations, including pharmacists, nurses, and home health care nurses.

8. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a human factors study to assess user comprehension of the label's instructions to use an inline filter with pore size of 1.2 microns during administration of Clinolipid (lipid injectable emulsion, USP) 20% or an admixture containing Clinolipid (lipid injectable emulsion, USP) 20%. In addition, the study should evaluate the ability of the user to appropriately spike the product's administration port. The study should enroll representative user populations, including pharmacists, nurses, and home health care nurses.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

10. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 204508
Product Name: CLINOLIPID

PMR/PMC Description: Randomized controlled trial to evaluate the risk of developing essential fatty acid deficiency (EFAD) in pediatric patients, including neonates, receiving either Clinolipid (lipid injectable emulsion, USP) 20% or standard of care soybean oil based lipid emulsion. Full essential fatty acid profiles should be evaluated according to standards set by major national reference laboratories. Genetic polymorphisms in the fatty acid desaturase genes (FADS) FADS1 and FADS2 should be determined in at least a subset of patients. The cut-off values for EFAD (e.g., suspected, mild and severe) should be established prior to the study. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR ####-4.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2014</u>
	Study/Trial Completion:	<u>09/2016</u>
	Final Report Submission:	<u>03/2017</u>
	Other:	<u>MM/DD/YYYY</u>

11. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

CLINOLIPID 20% will be approved in adults only where the consequences of EFAD are less of a concern (ie, reversible without clinical sequelae). However, the ability of CLINOLIPID to supply adequate amounts of EFA in pediatric patients is unknown and it is expected that CLINOLIPID will ultimately be used in this population regardless of whether it is ultimately approved.

12. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

It is possible that CLINOLIPID will be administered to children and placed at risk of EFAD, since it remains unknown if CLIONLIPID can supply enough EFA. There was some evidence in premature infants that there may be inadequate amounts of EFA provided by CLINOLIPID.

13. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

14. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized controlled trial to evaluate the risk of developing Essential Fatty Acid Deficiency (EFAD) in pediatric patients, including neonates, receiving either Clinolipid or standard of care soybean oil based lipid emulsion.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

15. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 204508
Product Name: CLINOLIPID

PMR/PMC Description: Randomized controlled trial in pediatric patients, including neonates, comparing Clinolipid (lipid injectable emulsion, USP) 20% with a phytosterol-depleted formulation of Clinolipid (lipid injectable emulsion, USP) 20% and another standard-of-care lipid emulsion to evaluate the incidence of liver injury, including either parenteral nutrition-associated liver disease (PNALD) or intestinal failure-associated liver disease (IFALD). This trial should be initiated after the results from PMRs #####-1, ###-2, and #####-6 are available. The phytosterol content of the phytosterol-depleted formulation of Clinolipid (lipid injectable emulsion, USP) 20% should be documented using validated analytical assay methods developed under PMRs #####-1. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR #####-4.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/2016
	Study/Trial Completion:	03/2019
	Final Report Submission:	09/2019
	Other:	MM/DD/YYYY

16. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Clinolipid contains phytosterols (plant derived sterols) as impurities. Published data has suggested a possible association between intravenously administered phytosterols and the development of liver injury, particularly in the pediatric and neonatal population. Although CLINOLIPID will be approved in adults, due to drug shortages and anticipated medical practice, CLINOLIPID is likely to be used in the pediatric population.

17. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Clinolipid contains phytosterols (plant derived sterols) as impurities. Published data has suggested a possible association between intravenously administered phytosterols and the development of liver injury, particularly in the pediatric and neonatal population. Although CLINOLIPID will be approved in adults, due to drug shortages and anticipated medical practice, CLINOLIPID is likely to be used in the pediatric population.

18. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

19. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized controlled trial in pediatric patients, including neonates, comparing Clinolipid with a phytosterol-depleted Clinolipid formulation and another standard-of-care lipid emulsion to evaluate the incidence of liver injury, including either Parenteral Nutrition-Associated Liver Disease (PNALD) or Intestinal Failure-Associate Liver Disease (IFALD).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other

20. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 204508
Product Name: CLINOLIPID

PMR/PMC Description: Randomized clinical trial in hospitalized patients receiving either Clinolipid (lipid injectable emulsion, USP) 20% or other standard-of-care IV lipid emulsions to evaluate clinical safety outcomes of sepsis and mortality. In addition, the trial will evaluate the requirement for ventilator support and length of stay in ICU and hospital.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2017</u>
	Study/Trial Completion:	<u>10/2018</u>
	Final Report Submission:	<u>04/2019</u>
	Other: _____	<u>MM/DD/YYYY</u>

21. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

CLINOLIPID has been shown to be an adequate source of calories in patients who require parenteral nutrition. However, its effect on clinical safety outcomes has not been fully characterized.

22. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Administration of parenteral nutrition is associated with a number of safety concerns. CLINOLIPID's effect on clinical safety outcomes has not been adequately evaluated and need to evaluate risks of sepsis and mortality.

23. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

24. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized clinical trial in hospitalized patients receiving either Clinolipid or other standard-of-care IV lipid emulsions to evaluate clinical safety outcomes of sepsis and mortality.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

25. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA# 204508
Product Name: CLINOLIPID

PMR/PMC Description: Randomized clinical trial comparing Clinolipid (lipid injectable emulsion, USP) 20% to another standard-of-care IV lipid emulsion, evaluating long-term risk of developing essential fatty acid deficiency (EFAD) and parenteral nutrition associated liver disease (PNALD) in patients receiving chronically-administered total parenteral nutrition (TPN). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR #####-4.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2014</u>
	Study/Trial Completion:	<u>03/2017</u>
	Final Report Submission:	<u>10/2017</u>
	Other:	<u>MM/DD/YYYY</u>

26. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Longer term (years) data is needed on the safety of chronically administered CLINOLIPID.

27. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

It has not been shown if CLINOLIPID supplies adequate amounts of EFA in patients receiving it long-term [to prevent essential fatty acid deficiency (EFAD)]. Long term parenteral nutrition is associated with parenteral nutrition associated liver disease (PNALD) and the contribution of CLINOLIPID to this risk is unknown. The contribution of phytosterols (impurities in CLINOLIPID) to the development of PNALD is also unknown.

Please note that for purposes of the template PNALD is to assess “known serious risk” in the adult population and EFA deficiency is to assess a “signal of serious risk” in patients receiving long-term PN.

28. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

29. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized clinical trial comparing Clinolipid to another standard of care IV lipid emulsion, evaluating long-term risk of developing essential fatty acid deficiency (EFAD) and parenteral nutrition associated liver disease (PNALD) in patients receiving chronically-administered TPN.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

30. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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

/s/

ROBERT FIORENTINO
10/03/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	CLINOLIPID (Lipid Injectable Emulsion), for intravenous use
Applicant	Baxter Healthcare Corp.
Application/Supplement Number	NDA 204508
Type of Application	Original Submission
Indication(s)	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
Established Pharmacologic Class ¹	lipid emulsion
Office/Division	ODE III/DGIEP
Division Project Manager	Matthew Brancazio
Date FDA Received Application	January 3, 2013
Goal Date	October 3, 2013
Date PI Received by SEALD	October 2, 2013
SEALD Review Date	October 2, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Top margin is greater than 1/2 inch.*

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- NO** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *The Indications and Usage; Dosage and Administration; Dosage Forms and Strengths; Drug Interactions; and, Use in Specific Populations headings are not in the center of the horizontal line (i.e., line should be equal distance from the right and left side of the heading).*

- NO** 4. White space must be present before each major heading in HL.

Comment: *There must be white space between the Patient Counseling Information statement and the revision date.*

- NO** 5. 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).

Comment: *The reference for each bulleted item in the Boxed Warning is missing. The reference "(6.1)" is missing at the end of the statement for the most common adverse reactions.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

NO

12. All text must be **bolded**.

Comment: *The statement "See full prescribing information for complete boxed warning" and text in the Boxed Warning are not bolded. Must bold.*

YES

Selected Requirements of Prescribing Information

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Selected Requirements of Prescribing Information

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- NO** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: Delete ". . . (b) (4)

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: Revision date must be "Revised: October 2013" not "Revised: mm/yyyy]."

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Selected Requirements of Prescribing Information

Comment: (1) In FPI, delete the colon (:) after subsection heading 2.3; (2) In FPI, do not underline subsection heading 2.4; (3) Delete subsection "6.3 Class Reactions" from TOC. Subsection 6.3 is not in the FPI; (4) In FPI, for subsection 12.1, the word "Action" must have "A" (upper case) instead of "a" (lower case); (5) In FPI, for subsection 13.1, the words "Mutagenesis", "Impairment", and "Fertility" must have "M", "I", and "F" (upper case) instead of "m", "i", "f" (lower case); (6) In FPI, for subsection 13.2, the words "Toxicology" and "Pharmacology" must have "T" and "P" (upper case), not "t" and "p" (lower case).

- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: The title for the Boxed Warning is not bolded and must be bolded. Also, it appears in a rectangular box. Do not put the boxed warning title in a box. It should be placed immediately above Indications and Usage section in the TOC. Do not insert extra space above and below the boxed warning title.

- NO** 32. All section headings must be **bolded** and in UPPER CASE.

Comment: In the TOC, section 5 must be "WARNINGS AND PRECAUTIONS", not "WARNINGS and PRECAUTIONS."

- NO** 33. All subsection headings must be indented, not bolded, and in title case.

Comment: The subsection headings in the TOC are not indented.

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "FULL PRESCRIBING INFORMATION".

Comment:

- NO** 37. All section and subsection headings and numbers must be **bolded**.

Comment: In the FPI, subsection 2.1 and section 17 are not bolded.

- NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS

Selected Requirements of Prescribing Information

4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: In the FPI, section 17 *PATIENT COUNSELING INFORMATION* is not numbered. Insert number "17" in front of the section heading.

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- NO** 42. All text is **bolded**.

Comment: The text in the *BOXED WARNING* is not bolded.

Selected Requirements of Prescribing Information

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

JEANNE M DELASKO
10/03/2013

LAURIE B BURKE
10/03/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 204508	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Clinolipid Established/Proper Name: Lipid Injectable Emulsion, USP, 20% Dosage Form: Emulsion, Injection Strengths: 20%		
Applicant: Baxter Healthcare Corporation		
Date of Receipt: January 3, 2013		
PDUFA Goal Date: October 3, 2013		Action Goal Date (if different):
RPM: Matt Brancazio, Pharm.D.		
Proposed Indication(s): 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.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	Nonclinical toxicology
NDA 18449 Intralipid 20% Lipid Emulsion	Indications and Usage; Dosage and Administration; Warnings and Precautions; Adverse Reactions; Use in Specific Populations; Clinical Pharmacology; Nonclinical Toxicology

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant provided a side-by-side comparison of the active ingredients with a scientific justification that the active ingredients in the listed products/literature are comparable to the active ingredients (fatty acids, essential and non-essential) in the proposed products. A formal pharmacokinetic bridging for all active ingredients (fatty acids, essential and non-essential) was not found to be necessary. For active ingredients in solution given parenterally, bioavailability/bioequivalence studies are generally not required.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
 YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
 YES NO
If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Intralipid 20% Lipid Emulsion	18449	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
 N/A YES NO
*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".
 If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:
 a) Approved in a 505(b)(2) application?
 YES NO
If "YES", please list which drug(s).
 Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?
 YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides a new mixture of "oils" to provide the necessary calories and essential fatty acids. Intralipid 20% is 100% soybean whereas Clinolipid* is a mixture of olive oil and soybean oil (~80%/20%); however, it is not a new molecular entity because the active ingredients (i.e., essential fatty acids) are those found in products already marketed, including Intralipid. The indication, dosage form, dosing, and all other aspects do not differ from Intralipid 20%.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled

syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: [NDA 204508](#)

Application Type: New NDA

Name of Drug: [ClinOleic 20% Lipid Intravenous Emulsion, USP](#)

Applicant: Baxter Healthcare Corporation

Submission Date: January 3, 2013

Receipt Date: January 3, 2013

1.0 Regulatory History and Applicant's Main Proposals

NDA 204508 is the first submission as an NDA for this product and is following the 505(b)(2) regulatory pathway for approval (RLD Intralipid by Fresenius Kabi). The NDA references PIND 74881 (no clinical studies conducted). One Pre-NDA meeting was held on July 13, 2011 on the requirements to support submission of ClinOleic 20% in the U.S.. This product is registered in numerous countries outside the U.S. including Canada, Australia, China, etc. The indication is for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. ClinOleic 20% Lipid Emulsion is the first non-100% soybean lipid emulsion product with a composition comprised of olive oil (~80%) and soybean oil (~20%). This drug class is considered in shortage by the FDA.

Note: This review was completed on February 20, 2013; however, was not placed into DARRTS at the time.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 60-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by March 18, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment: *Between Drug Interactions and Use in Specified Populations, there is NOT a space.*

- NO** 5. 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).

Comment: *The Adverse Reactions HL does not reference another section.*

Selected Requirements of Prescribing Information (SRPI)

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Initial approval of Intralipid 10% on October 7, 1975. should read: 1975*

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- NO** 12. All text must be **bolded**.
Comment: *Text other than heading is in normal font.*
- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- YES** 14. Must always have the verbatim statement “***See full prescribing information for complete boxed warning.***” centered immediately beneath the heading.
Comment:
- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “***See full prescribing information for complete boxed warning.***”)
Comment:
- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”
Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *There must be a white space between heading and this statement.*

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Extra bracket at end of YYYY*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment: *Not bolded correctly and the box surrounding is not necessary.*
- NO** 32. All section headings must be **bolded** and in UPPER CASE.
Comment: #5- "and" is not upper case
- NO** 33. All subsection headings must be indented, not bolded, and in title case.
Comment: *Subheadings are not indented*
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use

Selected Requirements of Prescribing Information (SRPI)

8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *The and in #5 does not match the CFR "AND"*

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- NO** 42. All text is **bolded**.
Comment: *Only "WARNING" is bolded. the remaining text is in normal font.*

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI)

N/A 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *Modification includes “... by MedDRA System Organ Class, then by Preferred Term in order of severity”*

Patient Counseling Information

N/A 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

MATTHEW B BRANCAZIO
10/03/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

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

Date: September 26, 2013

From: Jason To, Biomedical Engineer
CDRH/ODE/DAGRID/GHDB

To: Matt Brancazio
CDER/OND/ODEIII/DGIEP

Subject: CDRH Consult, ICC1300481, NDA 204508,
(DMF (b) (4) – Type III, CLARITY Container Closure System)

Mary Beth Esche, Associate Director – Global Regulatory Affairs
Baxter Healthcare Corporation
32650 North Wilson Road
Round Lake, IL 60073
Mailstop WG2-3S

Telephone: (224)270-4100
Fax: (224) 270-4119
Email: mary_beth_esche@baxter.com

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 204508. The device constituent of this combination product is the CLARITY container closure system, which consists of a (b) (4) Container configuration. Baxter has provided a Functional Validation Study for review as a follow up to a teleconference on August 29, 2013. This consult was requested in order for CDRH to provide a review of this study.

2. Device Description

CLARITY (b) (4) Container Packaging Components

(b) (4)



(b) (4)



The following figure below illustrates the CLARITY Container: (b) (4)



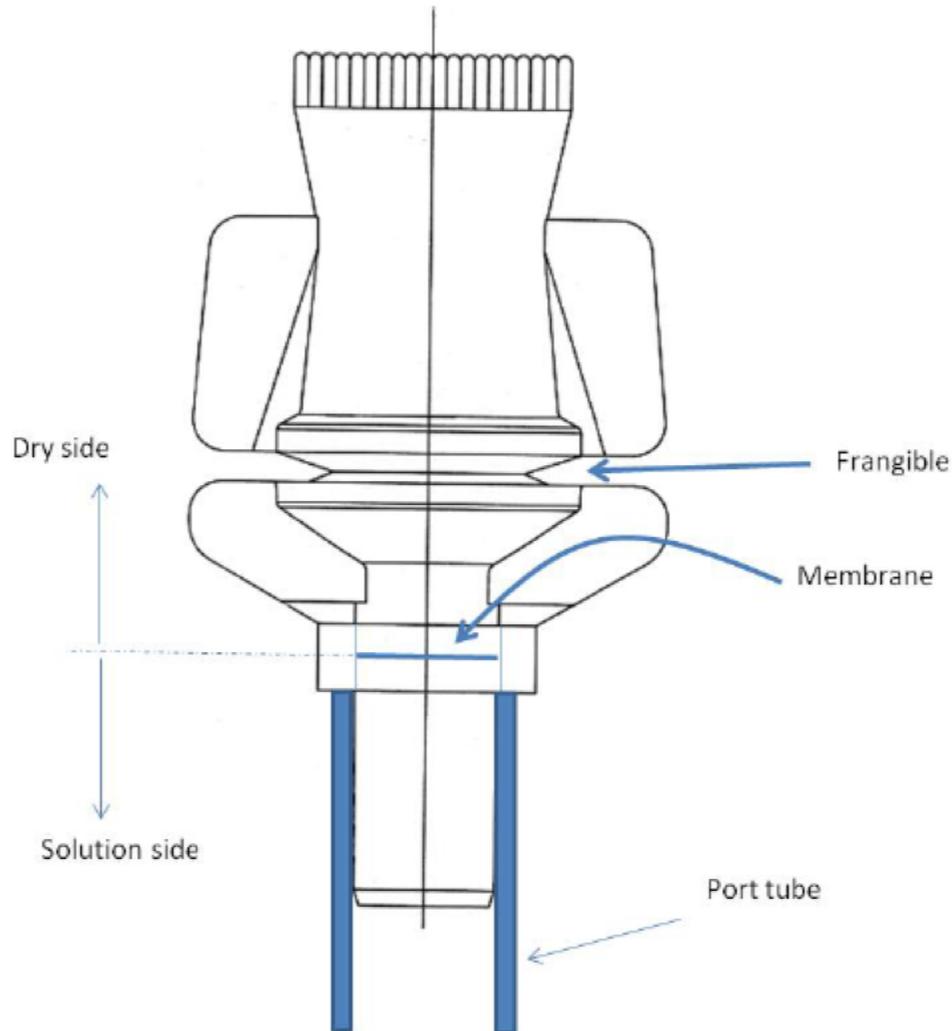
Port Tube

The container port tube is a (b) (4) component. The following is a diagram of the port tube:



Twist-Off Protector Closure

The administration port of the CLARITY (b) (4) Container is closed with a twist-off protector (TOP). This type of closure is (b) (4) (b) (4) to form the TOP closure. The following below illustrates the TOP closure:



Injection Site

The injection site closure is used to close the injection/medication port tube of the CLARITY (b) (4) Container. The injection site allows for (b) (4)

(b) (4)

(b) (4) The following below is a diagram of the injection site closure:



Secondary Packaging – Clear Overpouch

The secondary packaging is an (b) (4), (b) (4) clear overpouch. The (b) (4) clear overpouch consists of the following:

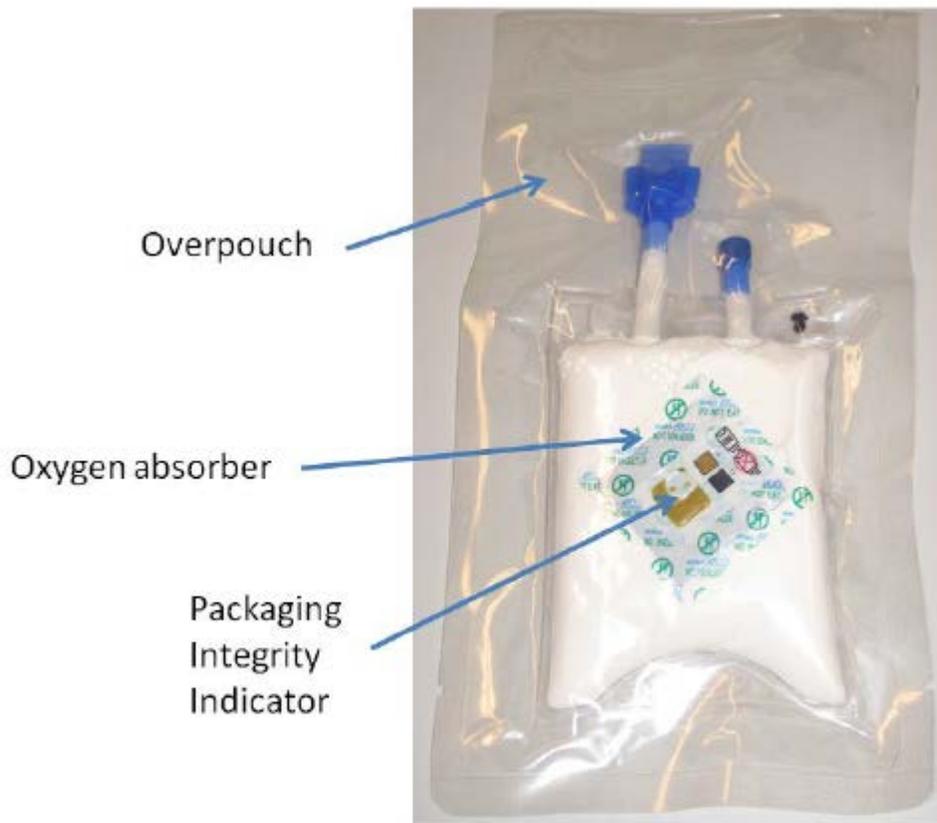
(b) (4)

Secondary Packaging – The Oxygen Absorber & Packaging Integrity Indicator

The oxygen absorber is a sachet (b) (4) containing an oxygen absorbing mixture composed primarily from (b) (4). The mixture is packed in a sachet made from (b) (4). The aim of the oxygen absorber is to absorb the small amount of oxygen ingress that occurs during the shelf life of the drug product.

The packaging integrity indicator (b) (4) consists of a label attached to the oxygen absorber sachet and contains an oxygen indicating mixture based on (b) (4). The oxygen indicating mixture has a clear change in color between the oxidized form (blue) and the reduced form (yellow). This change of color can be visually observed through the overpouch and is explained on the indicator itself. The indicator instructs the user not to use the product if the color of the oxygen indicating mixture does not correspond to the reference color printed next to the OK symbol on the label. The indicator allows for visual identification of the packaging integrity loss.

The following below illustrates the secondary packaging components for the CLARITY (b) (4) Container:



3. Documents Reviewed

Baxter "Verify U.S. Spikes performance when interacting with (b) (4) administration Lipid (b) (4) Study Number: 64965

4. CDRH Review and Comments

This CDRH review of the device constituent for this combination product in this particular consult consisted of only a review of the performance aspect of the study provided by the sponsor: Baxter “Verify U.S. Spikes performance when interacting with (b) (4) administration Lipid (b) (4)” Study Number: 64965

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

Baxter “Verify U.S. Spikes performance when interacting with (b) (4) administration Lipid (b) (4) Study Number: 64965

The purpose of this study was to verify that a defined list of U.S. Spikes comply with a set of requirements for the (b) (4) administration site (Twist off protector closure) as represented by the Clarity Lipid (b) (4). The system requirements that were verified through this protocol are the following:

For Direct Administration and Dispensing (b) (4) products:

- No leak (a detached droplet) during insertion
- No sliding out of the spike after (b) (4) submitted to a force of (b) (4) (Retention test).
- No sliding out/withdrawal of the spike after (b) (4) hanging.
- No leak (a consistent stream of bubbles) when internal pressure of (b) (4) kPa is applied for (b) (4).
- Insertion force shall be equal or greater than (b) (4)
- Removal force shall be equal or greater than (b) (4)
- Fragmentation: spike insertion in 50 units (one insertion per unit) shall not generate more than 5 visible fragments (diameter equal or greater than (b) (4)) in total after the solution has been filtered on a (b) (4) μm pore size membrane.

For Gravity and Automated compounding products:

- No leak (a detached droplet) during insertion
- No fall out (withdrawal) of the spike, no leak (dripping fluid) at the spike-administration site junction and no visible fragmentation (diameter equal or greater than (b) (4))
- Insertion force shall be equal or greater than (b) (4)
- Removal force shall be equal or greater than (b) (4)

Spike Insertion

The results of the testing indicate that the acceptance criteria was met for 6 of the 9 series tested.

Part Number (P/N) Description	Sample Size	Insertion Force (N)				Acceptance Criteria (Pass/fail)
		Mean (N)	STDEV (N)	k	UTL (N)	
(b) (4)						

Spike Removal

The results of the testing indicate that the acceptance criteria was met for 8 of the 9 series tested.

Part Number (P/N) Description	Sample Size	Removal Force (N)				Acceptance Criteria (Pass/fail)
		Mean (N)	STDEV (N)	k	LTL(N)	
(b) (4)						

Coring/Fragmentation

The results of the testing indicate that the acceptance criteria was met for all of the spikes tested. No coring/fragmentation were observed during testing.

Fall Out/Leak

- For Direct Administration and Dispensing ^{(b) (4)} products, the results of the testing indicate that the acceptance criteria was met for all the spikes tested for Fall Out. No movement or withdrawals of the spikes were observed during testing.
- For Gravity Compounding product code 2C0463, the results of the testing indicate that the acceptance criteria was met for this code. No leak or fall out spikes were observed during testing.
- For Gravity Compounding product code 2B8114, the results of the testing indicate that the acceptance criteria was met for this code for fall out. No withdrawal or movement of the spikes was observed during testing. However, droplets were observed on three spikes. Therefore, the acceptance criteria for the leak were not met for this test. The spikes that had the failure were inserted up to the flange (fully seated) into TOP. The droplets appear at the start of insertion.

Automated Compounding/Filling

- For Automated Compounding, the results indicate that the acceptance criteria was met. There was no leak, fall out, or fragmentation observed during testing. All delivery volumes as indicated by the compounder were within the +/- 5% accuracy specification and there no alarms during pumping, indicating the absence of any flow issues.
- For Automated Filling, the results indicate that the acceptance criteria was met. There were no leak, fall out, or fragmentation observed during testing. All delivery volumes were within the +/- 3% accuracy specification indicating the absence of any flow issues.

Summary of Results per Part Number

Usage	Test Part Number	Insertion Force Mean (N)	Removal Force Mean (N)	Fall Out (24 Hours) leak and Fragmentation	Fall out (5 hours) and Leak	Gravity Compounding Fall out / Leak / fragmentation	Automated Compounding Fall out / Leak / fragmentation	Automated Filling Fall out / Leak / fragmentation
Direct Administration	(b) (4)							

Usage	Test Part Number	Insertion Force Mean (N)	Removal Force Mean (N)	Fall Out (24 Hours) leak and Fragmentation	Fall out (5 hours) and Leak	Gravity Compounding Fall out / Leak / fragmentation	Automated Compounding Fall out / Leak / fragmentation	Automated Filling Fall out / Leak / fragmentation
Dispensing Gravity Compounding	(b) (4)					(b) (4)		
Automated Compounding & Filling Note: Refer to section 8 for investigation related to these particular series	(b) (4)						(b) (4)	

Review Analysis:

Upon review of the information provided, the following questions were sent from CDRH to CDER on September 26, 2013 to convey to the sponsor to address. The sponsor's responses to the deficiencies were received on September 27, 2013.

The sponsor states that Study 64965 was a functional test rather than a usability study, and acknowledges that the observations and failures that were documented in the study need to be further addressed. The firm states

that in order to make spike interface recommendations, further assessment of this study will take place in the form of an Interface Evaluation and Recommendation Report.

- 1) *FDA Question:* 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) ExactaMix Inlet Ref: 174) failed and did not meet the acceptance criteria for spike removal. Please 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.

Sponsor Response: As stated in the second bullet of Section 8 of report 64659, the investigation into the failure of the spike removal force with the (b) (4) found that one of the 118 units was defective as it was not (b) (4). An investigation is ongoing for this issue. Upon retesting with a (b) (4) spike the reanalyzed data passed.

- 2) *FDA Question:* 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. Please provide a detailed rationale and justification for why the leak failure is considered acceptable.

Sponsor Response: For the results discussed in Section 5.3.3.1 of the final report, the lipid drops noted were documented as observations only and were not part of the acceptance criteria for this aspect of the Fall Out test. This observation made within the final report for Study 64965 is to be further assessed within the proposed ClinOleic Interface Evaluation and Recommendation Report.

As a point of clarification, Section 5.3.3.2 of the final report addresses the aspect of the Fall Out test where leaks were a specific part of the acceptance criteria. A leak in this test was defined as a consistent stream of bubbles. No leaks were observed during this test.

- 3) *FDA Question:* 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. Please provide a detailed rationale and justification for why the leak failure is considered acceptable.

Sponsor Response: The failures of 2B8114 for leaks and insertion force made within the final report for Study 64965 are to be further assessed

within the proposed ClinOleic Interface Evaluation and Recommendation Report.

- 4) FDA Question: You provided study number 64965 Baxter “Verify U.S. Spikes performance when interacting with [REDACTED] (b) (4) administration Lipid [REDACTED] (b) (4). Please explicitly state what spikes were verified to meet your requirements for the [REDACTED] (b) (4) administration site (Twist off protector closure) as represented by the Clarity Lipid [REDACTED] (b) (4) (Clinoleic 20%), and what spikes did not meet your requirements.

Sponsor Response: All failures and observations made within the final report for Study 64965 are to be further assessed within the proposed ClinOleic Interface Evaluation and Recommendation Report.

5. CDRH Conclusion

Based on the review of the information provided by the sponsor, interaction between CDRH and CDER, as well as the interaction between FDA and the firm, the sponsor's responses are insufficient. The firm will need to adequately address the outstanding deficiencies outlined in this review. Please also defer to the Human Factors review as well.

If you have any questions, please contact Jason To at (301) 796 - 6297.

Sincerely,

Jason To -
S

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Jason To
Biomedical Engineer

Concurred By:

Sajjad H.
Syed

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Chief, General Hospital Devices Branch

Keith G.
Marin -S

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Keith Marin
Combination Products Team Leader

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/s/

MATTHEW B BRANCAZIO

10/01/2013

Administratively checked into DARRTS for CDRH GHDB reviewer, Jason To.



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

DATE: September 26, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Matt Brancazio, Regulator Project Manager, CDER/OND/ODEIII/DGIEP

SUBJECT: NDA 204508
Applicant: Baxter Healthcare
Drug: Clinolipid, Lipid Injectable Emulsion, 20%, USP
Device: Nutritional Bags
Intended Use: Parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated
CTS Tracking: ICC1300367/CON1315280

CDRH Human Factors Review

Review Materials:

The following global link is the electronic submission of the NDA:

EDR: <\\cdsesub1\EVSPROD\NDA204508\204508.enx>

The following link is a link to the eRoom

http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_33d53

Submission: <\\CDSESUB1\evsprod\NDA204508\0014\m1\us\cover-letter.pdf>

Overview and Recommendation

The Division of Gastroenterology and Inborn Errors Products, Office of New Drugs, Center for Drug Evaluation and Research requested a human factors consultative review to evaluate Baxter's study results in addressing the potential for particles from the bag material to enter the solution, and to recommend any further actions. The device is a parenteral feeding bag to provide source of calories and essential fatty acids when oral and enteral nutrition is not possible, insufficient, or contraindicated.

NDA 204508 is a priority review with PDUFA goal date of October 3, 2013. On Tuesday, July 16, 2013, a Health Canada MedEffect e-notice was released with the following information for Clinoleic (Baxter) 20% - Potential for the Presence of Particles from the Administration Port Material. During the preparation of Clinoleic 20% for parenteral nutrition, there is potential for particles from the bag material to enter the solution. Administration sets provided with Clinoleic 20% should include a 1.2 micron filter to reduce the risk of particles entering the tubing. Baxter has since submitted the following response to the FDA and DGIEP is requesting the involvement of CDRH Human Factors to evaluate the results of their planned study as well as

recommend any further actions. It should be noted that the planned study does not appear to be related to human factors but rather performance evaluation of the device.

Background Information: Baxter Canada received several complaints regarding generation of particulate matter upon spiking the ClinOleic bag with one compounding set and one administration sets. Baxter indicated that a full investigation is currently underway, however the initial investigation revealed that the particle found in each of these cases was the entire membrane disc from the twist off protector closure. Baxter is performing additional analysis on past Clinoleic complaints to determine if there are correlations to things such as spike geometry. A study is currently being designed to duplicate the TOP membrane separation such that Baxter can better understand the exact parameters leading to a separated TOP. The full investigation will be completed prior to Clinolipid launch in the US. A Medical Risk Assessment was also conducted to review the situation and the risk was deemed to be low as 1.2 micron in-line filters are recommended by ASPEN/ESPEN and are typically used to administer lipids. Health Canada requested a DHP letter to remind clinicians to use a 1.2 micron filter when administering lipids to patients.

DGIEP and Baxter held a telephone conference on August 29th to better understand the problems occurring in Canada. During this discussion, Baxter stated that the contributing factors may be the geometrical interface between a specific spike, and method of spiking i.e. amount of twisting depending on the length of the spike, and amount of force being generated by the user. As part of the investigation, Baxter has generated a report (R4port # 64965) that verified a defined list of US spikes and their compliance with a set of requirements for (b) (4) administration set (with twist off protector closure) as represented in the (b) (4) (Clinoleic 20%). Baxter indicated that this report should provide information on the appropriate spike that users should use. Note that this report included specific values of force generated during insertion; however, there was no analysis of how these forces are correlated to forces that a user may generate that may result in particles generation and membrane dislodgement. In addition, Baxter indicated that the immediate fix to this problem is to inform clinicians to use an in-line filter that is provided as part of the administration set. This is also considered standard practice for home total parenteral nutrition.

Because Baxter confirmed that there are in-line filters that are provided for home users, and based on internal discussion with medical officer in CDRH, we believe this may resolve our concern regarding particle generation during spiking and to prevent TOP membrane dislodgement in the home setting. However, we believe that labeling should be used to help assure that filter use is mandatory in hospitals/ institutions i.e. providing precautions and statements about using appropriate filters and spikes. We remained concerned that the TOP membrane could curl up like a straw and slip right into a central line without a filter. Although users may notice the TOP membrane floating on top of the solution, the fluid is opaque and the bag is stored and transported flat, not upright, so they might not notice it. In addition, we are unclear if the labeling will provide users a list of possible spikes that can be used for the proposed parenteral bags.

Recommendation: Because the above potential solutions are in direct response to addressing known hazard of particle generation and membrane dislodgement during, CDRH HF needs to review human factors validation data that demonstrate that representative users: (1) understand the potential hazard, (2) recognize appropriate spikes to be used with their product, (3) understand that the use of in-line filters is necessary, (4) use appropriate spike and filter properly during product set-up, (5) verify after set-up to make sure that there are no particles being generated that can result in patient harm, and that the membrane is still intact.

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QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ronald D. Kaye -S

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

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/s/

MATTHEW B BRANCAZIO

09/30/2013

Administratively entered into DARRTS for CDRH HF reviewer

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

Memorandum

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

Date: September 17, 2013

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

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

Subject: NDA 204508
OPDP Comments for draft Clinolipid 20% (lipid injectable emulsion, USP),
for intravenous use, carton and container

OPDP has reviewed the proposed draft carton and container labeling for Clinolipid 20% (lipid injectable emulsion, USP), for intravenous use. We have reviewed the draft carton and container labeling, sent to us on September 11, 2013, and have no comments at this time.

Thank you for the opportunity to comment on the proposed carton and container labeling.

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

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

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/s/

MEETA N PATEL
09/17/2013



Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date: September 6, 2013

From: Alyson Karesh, MD, Medical Officer
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Pediatric Team Leader
Lynne Yao, MD OND Associate Director
Pediatric and Maternal Health Staff (PMHS)

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

NDA: 204508

Sponsor: Baxter Healthcare Corporation

Drug: ClinOleic 20%

Proposed Indication: Parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Division Consult Request: a) Confirm PREA does not apply to this application.
b) Assist with labeling for both pediatric and maternal health.
c) Assist with potential (non-PREA) PMRs in pediatric and neonatal patients.¹

Summary:

See prior PMHS consult, July 13, 2011² for background and the full PMHS assessment of the available pediatric data on this product. Briefly, PMHS concluded:

¹ NDA 204508, ClinOleic 20%, Pediatric and Maternal Health Staff Request for Consultation, March 11, 2013.

“in order to extrapolate efficacy to the pediatric population, the primary division must be comfortable that there are two adequate and well-controlled studies in adults supporting dosing, safety, and efficacy. On face, the submitted pediatric studies do not appear to be sufficient to demonstrate effectiveness or safety.

- Studies must be performed in children using adequate and consistent dosing of lipids (2-3 g/kg/day).
- Studies will need to address the full age span (preterm and term neonates, toddlers, children, and adolescents).
- If efficacy cannot be extrapolated, studies in pediatric patients must demonstrate growth and adequate maintenance of nutritional parameters (anthropomorphic measurements, prealbumin, hemoglobin, essential fatty acids, fat soluble vitamin levels)
- Additional long- term safety data is needed in a sufficient number of patients. Careful attention must be paid to monitoring of essential fatty acids, coagulation studies, transaminases, fat soluble vitamins, triglyceride levels, and lipid profiles.”²

For this consult, PMHS participated in numerous team meetings discussing the potential approval of this product, [REDACTED] ^{(b) (4)} The pediatric team of PMHS confirmed that PREA will not be triggered by the approval of this product.

DGIEP has concluded extrapolation of efficacy from adults to pediatric patients can be considered and pediatric dosing can be based on existing literature guidelines. The major concerns for an adult approval the current review cycle concern the delivery of the product (e.g., the bag leaking), not the product itself.

Discussion:

[REDACTED] ^{(b) (4)}

[REDACTED]

Proposed Postmarketing Requirements (Commitments):

PMHS agrees with DGIEP’s plan to evaluate creating postmarketing requirements (under FDAAA) or postmarketing commitments to obtain pediatric data. The pediatric data requirement and/or commitment should take into consideration the potentially heterogeneous pediatric population that would benefit from this product. For example, the safety concerns for a premature infant who is receiving chronic total parental nutrition

²IND 74881, ClinOleic 20%, Pediatric and Maternal Health Staff Memorandum, July 13, 2011, reference ID 2972417.

(TPN) and IV lipid emulsion may be different than a 10 year-old child on chronic TPN and IV lipid emulsion while awaiting a liver transplant.

Given the upcoming public meeting on October 29, 2013 on the topic of IV lipid emulsion products, PMHS agrees with DGIEP's plan word the PMRs for this product broadly, with the intention of being more specific with the protocol at a later date. The current draft PMR's (as in Appendix I) appear reasonable to PMHS.

Proposed labeling:

When a product is not approved for pediatric use, all pediatric information should be placed in Subsection 8.4, unless a safety issue rises to the level of Warnings and Precautions or Contraindications .

“If a specific risk has been identified for pediatric patients, this risk information must be described in the Pediatric Use subsection and, if appropriate, placed in the Contraindications section or Warnings And Precautions section. In such cases, the Pediatric Use subsection must refer to the risk information in the Contraindications or Warnings and Precautions section, as required by regulation (21 CFR 201.57(c)(9)(iv)(B), (E), and (F)).”³

(See 21 CFR 201.57(c)(9)(iv)(D) or (E). or see Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products labeling, draft guidance February 2013.)

Presuming ClinOleic 20% will not be approved for use in any pediatric age group in the current review cycle, PMHS has the following labeling recommendations:

a. Indication

Because this particular IV emulsion product will not be approved for pediatric use and there is a potential safety concern of fatty acid deficiency, but Intralipid is approved and marketed for pediatric use, PMHS suggests that distinction between the two products be emphasized. The indication should clearly state that ClinOleic 20% is approved for adults only.

Additionally, since the risk of fatty acid deficiency is unique to this IV emulsion product, DGIEP may want to consider including explicit limitations of use for a part of, or all of, the pediatric population. PMHS acknowledges that if the shortage of Intralipid becomes significant, then having ClinOleic 20% available for pediatric patients will be important. However, if the anticipated availability of Intralipid will likely to be sufficient for the pediatric patients who require IV emulsion, then a limitation of use may be helpful to highlight the differences between Intralipid and ClinOleic 20%.

³Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products labeling, draft guidance February 2013. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM341394.pdf> , accessed September 3, 2013.

Current wording of the indication:

[REDACTED] (b) (4)

PMHS proposed wording of the indication (PMHS additions in blue):

ClinOleic 20% is a lipid emulsion 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.

Limitations of Use

[REDACTED] (b) (4)

b. Death in Preterm Infants

• Boxed Warning

This safety concern is a boxed warning in the Intralipid labeling (NDA 18449). Therefore, DGIEP should include a boxed warning for this same information for this product as well.

• Highlights

The language in the Highlights section regarding “Death in Preterm Infants” (5.1) should more strongly state the concern about use in preterm infants and not provide dosing guidance, since this product is not being approved for use in that population.

Current wording: [REDACTED] (b) (4)

PMHS proposed wording: **Death in preterm infants. (5.1)**

• Subsection 5.1, Death in Preterm Infants

PMHS suggests adding in a statement that the product is not approved for use in preterm infants, as that is a difference between this product and Intralipid.

PMHS proposed wording for Subsection 5.1 (PMHS additions in blue):

5.1 Death in Preterm Infants

Deaths in preterm infants after infusion of intravenous lipid emulsion have been reported in the medical literature.¹ Autopsy findings included intravascular lipid accumulation in the lungs.

ClinOleic 20% is not recommended for use in pediatric patients, including preterm infants. [REDACTED] (b) (4)

[REDACTED] (b) (4)
Preterm and small for gestational age infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid

emulsion infusion;

(b) (4)

c. Additional Safety Concerns

- As discussed above, in general, even when a product is not being approved for pediatric use, such as in this case, any safety concerns that rise to the level of Warnings and Precautions or Contraindications should be included in those respective sections of labeling. Therefore, subsection 8.4 should briefly describe the safety issue and cross-reference to the full description. PMHS defers to DGIEP's gastroenterology expertise for a determination of whether any safety concerns of particular relevance to the pediatric population would require a statement in Warnings and Precautions or Contraindications. For example, the issues of potential fatty acid deficiency, and physosterol-related risks, might be appropriate for inclusion in the Warnings and Precautions section of labeling.

Additionally, PMHS defers to DGIEP about the inclusion of other adverse reactions that warrant labeling but do not require a statement in Warnings and Precautions, such as Parenteral Nutrition-Associated Liver Disease (PNALD) or Intestinal Failure-Associated Liver Disease (IFALD). Any pediatric-related safety concerns that do not warrant inclusion in Warnings and Precautions or Contraindications should be included in subsection 8.4.

- Intralipid labeling contains a warning about aluminum toxicity. The Intralipid labeling includes the statement, "premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum."⁴ If ClinOleic 20% contains similar or greater levels of aluminum as Intralipid, then similar language should be included in the ClinOleic 20% labeling.
- Intralipid labeling Adverse Reactions, refers to thrombocytopenia in neonates.⁵ If the safety concern of thrombocytopenia in neonates applies to ClinOleic 20% as well (class labeling), then the safety concern should be included in subsection 8.4 of ClinOleic20% labeling. (See discussion 'd' below.)

d. Subsection 8.4, Pediatric Use

In the Pediatric Use subsection, 8.4, the lack of a pediatric approval should be clearly stated and contain cross-references to all other relevant information, such as the current warning of Death in Preterm Infants (5.1), the potential for fatty acid

⁴ Intralipid 20%, soybean oil, NDA 018449, April 24, 2007 labeling, accessed via Drugs@FDA, September 3, 2013.

⁵ Intralipid 20%, soybean oil, NDA 018449, April 24, 2007 labeling, accessed via Drugs@FDA, September 3, 2013.

deficiency information (5.x if the information is included in Warnings and Precautions), aluminum toxicity (5.x), phyosterol-related risks (5.x), and any other safety concerns of particular significance in the pediatric population (5.x).

PMHS proposed wording for Subsection 8.4:

8.4 Pediatric Use

The safety and effectiveness of ClinOleic 20% have not been established in pediatric patients. (b) (4)

Deaths in preterm infants after infusion of IV lipid emulsion have been reported [*See Death in Preterm Infants (5.1)*]. Patients, particularly premature infants, are at risk for aluminum toxicity [*See xxx (5.x)*]. Patients, including pediatric patients, are at risk for phyosterol-related adverse reactions [*See xxx (5.x)*]. (b) (4)

Conclusion:

Final labeling will be negotiated with the applicant and may not fully reflect the changes suggested here. See final approved labeling. PMHS will continue to work with DGIEP as they negotiate product labeling and write any pediatric postmarketing requirements and commitments.

APPENDIX I

Draft Postmarketing Requirements, as of September 4, 2013⁶

1. Randomized control trial to evaluate the risk of developing Essential Fatty Acid Deficiency (EFAD) in pediatric patients including neonates, receiving either Clinolipid or standard of care soybean oil based lipid emulsion.
2. Randomized controlled trial in pediatric patients including neonates comparing ClinoLipid with a phytosterol-depleted ClinoLipid formulation and another standard-of-care lipid emulsion to evaluate the incidence of liver injury, including either Parenteral Nutrition-Associated Liver Disease (PNALD) or Intestinal Failure-Associate Liver Disease (IFALD), should be the primary objective. This study should be initiated after the results from PMR #1 are available and can [REDACTED] (b) (4)
3. Randomized clinical trial in hospitalized patients receiving either Clinolipid or other standard-of-care lipid emulsions to establish the risk of [REDACTED] (b) (4) [REDACTED] (b) (4). Additionally, this study should evaluate clinical outcomes such as sepsis, requirement for ventilator support, timing of discharge, and mortality.
4. Randomized clinical trial evaluating long-term risk of developing EFAD and PNALD in patients receiving chronically-administered Clinolipid compared to other standard-of-care lipid emulsions.

⁶ Obtained from the DGIEP eroom, http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_39b92, accessed September 4, 2013.

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/s/

ALYSON R KARESH
09/06/2013

HARI C SACHS
09/09/2013
I agree with these recommendations.

LYNNE P YAO
09/09/2013



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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**PEDIATRIC AND MATERNAL HEALTH STAFF,
MATERNAL HEALTH TEAM REVIEW**

Date: 09-09-2013

From: Leyla Sahin, M.D.
Medical Officer,
Pediatric and Maternal Health Staff, Maternal Health Team

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

Through: Lynne P Yao, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Gastroenterology and Inborn Errors Products

Drug: ClinOlipid 20% (20% soybean oil, 80% olive oil lipid emulsion); NDA 204508

Applicant: Baxter Healthcare Corporation

Subject: Labeling for Pregnancy and Nursing Mothers

Materials Reviewed: Applicant submission, literature review

Consult Question: Please review the proposed labeling for Pregnancy and Nursing Mothers

INTRODUCTION

Baxter Healthcare Corporation submitted a 505(b) (2) application on January 3, 2013 for ClinOlipid® (20% soybean oil, 80% olive oil lipid emulsion) for parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition are not possible, insufficient, or contraindicated. This application was granted a priority review due to a shortage of lipid emulsion products. It is marketed in most European countries, Canada, Australia, and China. The referenced innovator product, Intralipid®, was approved in 1981, and is the only lipid emulsion product on the market. The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested the Pediatric and Maternal Health Staff, Maternal Health Team's (PMHS-MHT) review of the sponsor's proposed labeling for Pregnancy and Nursing Mothers. PMHS-MHT performed a literature search on parenteral lipid emulsion use in pregnancy and breastfeeding. This review summarizes available data, and provides conclusions and recommendations regarding Pregnancy and Nursing Mothers labeling for ClinOlipid.

BACKGROUND

Pregnant women may have a need for parenteral nutrition due to severe hyperemesis gravidarum¹ or other serious medical or surgical conditions where oral or enteral nutrition are not possible. Two families of essential fatty acids (fatty acids that humans cannot synthesize), omega-3 and omega-6, are essential for physiologic functions such as oxygen transport, energy storage, cell membrane function, and regulation of inflammation and cell proliferation.² The parent fatty acid for omega-3s is α -linoleic acid (ALA) and for omega-6s the parent fatty acid is linoleic acid (LA). LA is converted to the biologically active omega-6 fatty acid, arachidonic acid, which is involved in cell signaling pathways and functions as a precursor for pro-inflammatory eicosanoids. ALA is converted to eicosapentaenoic acid, which is converted to the omega-3 fatty acid, docosahexaenoic acid (DHA). DHA is the critical component of cell membranes in the brain and retina, where it is involved in visual and neural function as well as neurotransmitter metabolism. Data from observational studies and randomized controlled trials have supported the role of DHA in fetal and infant neurodevelopment.^{2,3,4} Clinical Guidelines recommend that pregnant and lactating women consume at least 200 mg of DHA per day.⁵ The American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant and lactating women consume two 6 ounce servings of fish per week in order to meet their DHA requirements.⁶ The required quantity of omega-6 fatty acids in pregnancy is not known³; therefore there are no established guidelines.

¹ ACOG Practice Bulletin number 52 Nausea and Vomiting of Pregnancy. April 2004.

² Coletta JM, et al. Omega-3 Fatty acids and Pregnancy. 2010. Reviews in Obstetrics and Gynecology 3(4):163-171.

³ Brenna JT, et al. Background Paper on Fat and Fatty Acid Requirements during Pregnancy and Lactation. Ann Nutr Metab. 2009;55:97-122.

⁴ Bernardi JM, et al. Fetal and Neonatal levels of Omega-3: Effects on Neurodevelopment, nutrition, and growth. The Scientific World Journal. 2012;202473.

⁵ Koletzko B, et al. World Association of Perinatal Medicine Dietary Guidelines Working Group. The roles of long chain polyunsaturated fatty acids in pregnancy, lactation, and infancy: review of current knowledge and consensus recommendations. J Perinatal Medicine. 2008;36:5-14.

⁶ Nutrition During Pregnancy. ACOG Patient Education Pamphlet September 2013.

http://www.acog.org/Resources_And_Publications/Patient_Education_Pamphlets/Files/Nutrition_During_Pregnancy

REVIEW OF DATA

Literature Review

Pregnancy

There is a published review of a case series of 32 women who received soybean or soybean/safflower based lipid emulsion treatment during pregnancy.⁷ The length of time each patient received lipid emulsion therapy ranged from 7 to 260 days. In 3 cases, treatment was initiated before conception and continued through the entire pregnancy. In 18 cases, treatment was initiated during pregnancy (timing of gestation not stated) and continued through delivery. In 2 cases, treatment was given intermittently during pregnancy and continued through delivery. Thirty infants were born without complications and had “normal developmental characteristics” (timing of follow up is not stated). There was no correlation between the administration of lipid emulsion and the onset of labor. The following are the abnormal outcomes reported:

- One infant was born with mild “hyaline membrane disease” as a result of prematurity. She was born at 30 weeks because of cardiac arrest and subsequent death of the mother as a result of diabetic complications, anemia, renal failure, and acute myocarditis.
- One infant was born with a partial cleft lip.
- There was one fetal death due to subarachnoid hemorrhage. The mother was a class D diabetic with peripheral neuropathy and retinopathy who experienced several episodes of gastrointestinal bleeding due to esophagitis. This death was felt to be due to the mother’s multiple medical complications, and not the parenteral nutrition.
- There was one infant death of that occurred 3 days post-delivery. The infant was born prematurely at 29 weeks, and died of sudden bradycardia and cyanosis. The mother was a class F diabetic whose pregnancy was complicated by gastroparesis, hemorrhagic gastritis, narcotic addiction, intrauterine growth restriction, and severe pre-eclampsia. Autopsy showed massive diffuse pulmonary hemorrhage, and the authors concluded that it was not due to parenteral nutrition.

Reviewer comments

PMHS-MHT had a discussion with DGIEP regarding whether these published data should be added to labeling. DGIEP and PMHS-MHT agreed that the data are too limited to support labeling changes.

Lactation

No publications on lipid emulsion therapy and breastfeeding were found in the literature.

LABELING

Applicant’s proposed labeling

⁷ Amato P, et al. A historical perspective and review of the safety of lipid emulsion in pregnancy 1991. Nutrition in Clinical Practice 6:189-192.

The following is the applicant's proposed labeling for ClinOlipid:

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with ClinOlipid 20%. It is also not known whether ClinOlipid 20% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ClinOlipid 20% should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether ClinOlipid 20% is (b) (4) in human milk. Because many drugs are (b) (4) in human milk, caution should be exercised when ClinOlipid 20% is administered to a nursing woman.

DISCUSSION AND CONCLUSIONS

There is only one publication of a case series in the literature regarding the use of soybean based lipid emulsion therapy during pregnancy. No safety issues were reported in the publication. The innovator product, Intralipid, which is the reference drug for this 505(b) (2) application, is labeled pregnancy category C based on the lack of reproductive and developmental toxicology data and lack of human data. PMHS-MHT had discussions with DGIEP regarding the content of Pregnancy and Nursing Mothers subsections of labeling. In concurrence with the DGIEP reviewers, PMHS-MHT agrees that the current regulatory language under Pregnancy, "ClinOlipid should be used during pregnancy only if clearly needed," adequately reflects the risk-benefit profile regarding use in pregnancy.

Clinolipid has only 20% of the linoleic acid (an omega-6 fatty acid) content of the reference product Intralipid. Whether the lower linoleic acid content would be of clinical significance during pregnancy was raised. Because the benefits of omega-6 fatty acids in pregnancy are not documented, it is not possible to determine the clinical significance of a lower linoleic acid content. PMHS-MHT recommends that the relevant section of Clinolipid labeling state clearly that the linoleic acid content is lower than the reference product; however, additional statements in the Pregnancy section of labeling are not warranted.

There are no human data on the use of lipid emulsions during lactation. The proposed language adequately reflects the risk-benefit decision regarding use in pregnancy.

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers labeling information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide

relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the labeling, not the amount.

LABELING RECOMMENDATIONS

Recommended additions are underlined and deletions are struck out. These revisions were agreed upon by PMHS-MHT and DGIEP.

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and/or well-controlled studies with ClinOlipid 20% in pregnant women. (b) (4) animal reproduction studies have not been conducted with ClinOlipid 20%. It is also not known whether ClinOlipid 20% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ClinOlipid 20% should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether ClinOlipid 20% is present (b) (4) in human milk. Because many drugs are (b) (4) present in human milk, caution should be exercised when ClinOlipid 20% is administered to a nursing woman.

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/s/

LEYLA SAHIN
09/09/2013

JEANINE A BEST
09/10/2013

LYNNE P YAO
09/10/2013

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

Memorandum

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

Date: August 27, 2013

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

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

Subject: NDA 204508
OPDP Comments for draft Clinolipid 20% (lipid injectable emulsion, USP),
for intravenous use, PI

OPDP has reviewed the proposed draft PI for Clinolipid 20% (lipid injectable emulsion, USP), for intravenous use. We have reviewed the draft PI, accessed from the eroom on August 27, 2013, and have the following comments.

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

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

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

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/s/

MEETA N PATEL
08/27/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

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

Date: July 31, 2013

From: Jason To, Biomedical Engineer
CDRH/ODE/DAGRID/GHDB

To: Matt Brancazio
CDER/OND/ODEIII/DGIEP

Subject: CDRH Consult, ICC1300298, NDA 204508,
(DMF (b) (4) – Type III, CLARITY Container Closure System)

Mary Beth Esche, Associate Director – Global Regulatory Affairs
Baxter Healthcare Corporation
32650 North Wilson Road
Round Lake, IL 60073
Mailstop WG2-3S

Telephone: (224)270-4100
Fax: (224) 270-4119
Email: mary_beth_esche@baxter.com

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 204508. The device constituent of this combination product is the CLARITY container closure system, which consists of a (b) (4) Container configuration. Baxter has provided a response to testing per ISO 15747 Annex A, “A.3 Resistance to Temperature Stability, Pressure, and Leakage” requested by FDA in a teleconference on May 20, 2013.

2. Device Description

CLARITY ^{(b) (4)} Container Packaging Components



The following figure below illustrates the CLARITY Container:

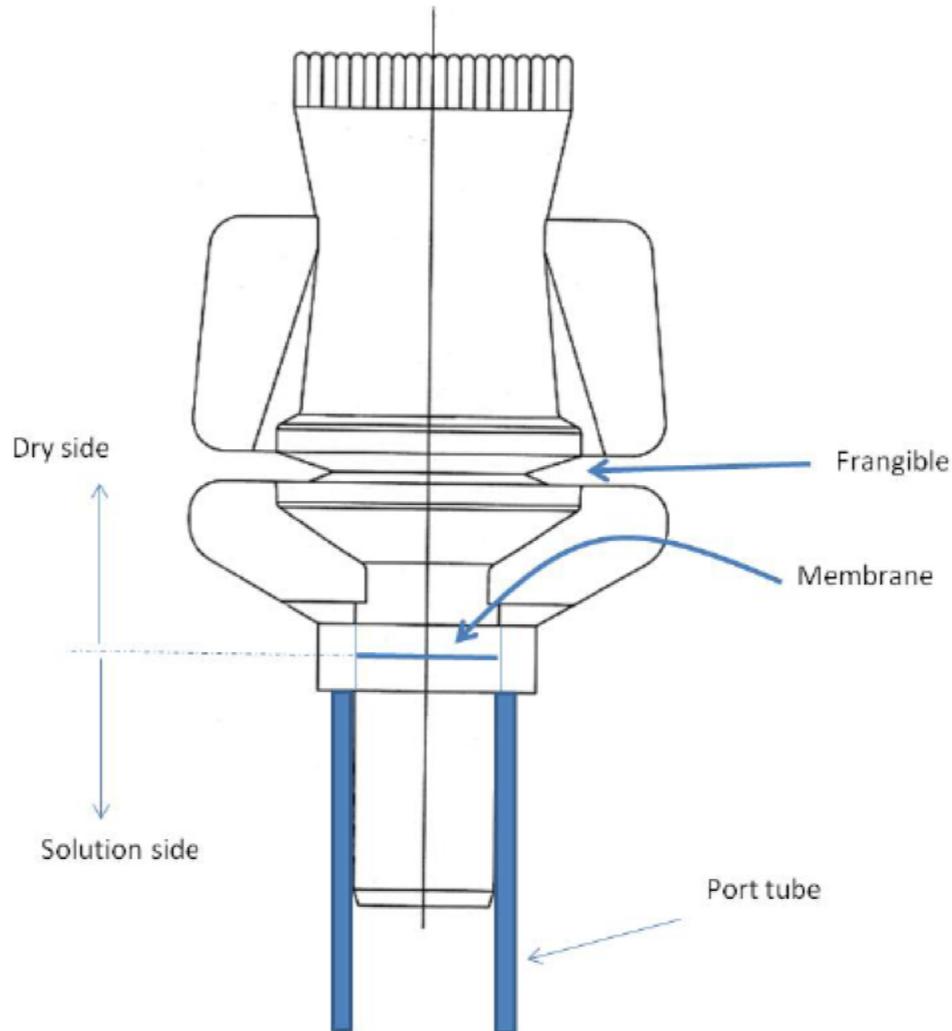
(b) (4)



(b) (4)

Twist-Off Protector Closure

The administration port of the CLARITY (b) (4) Container is closed with a twist-off protector (TOP). This type of closure is (b) (4) (b) (4) to form the TOP closure. The following below illustrates the TOP closure:



Injection Site

The injection site closure is used to close the injection/medication port tube of the CLARITY (b) (4) Container. The injection site allows for (b) (4)

(b) (4)

(b) (4). The following below is a diagram of the injection site closure:



Secondary Packaging – Clear Overpouch

The secondary packaging is an (b) (4), (b) (4) clear overpouch. The (b) (4) clear overpouch consists of the following:

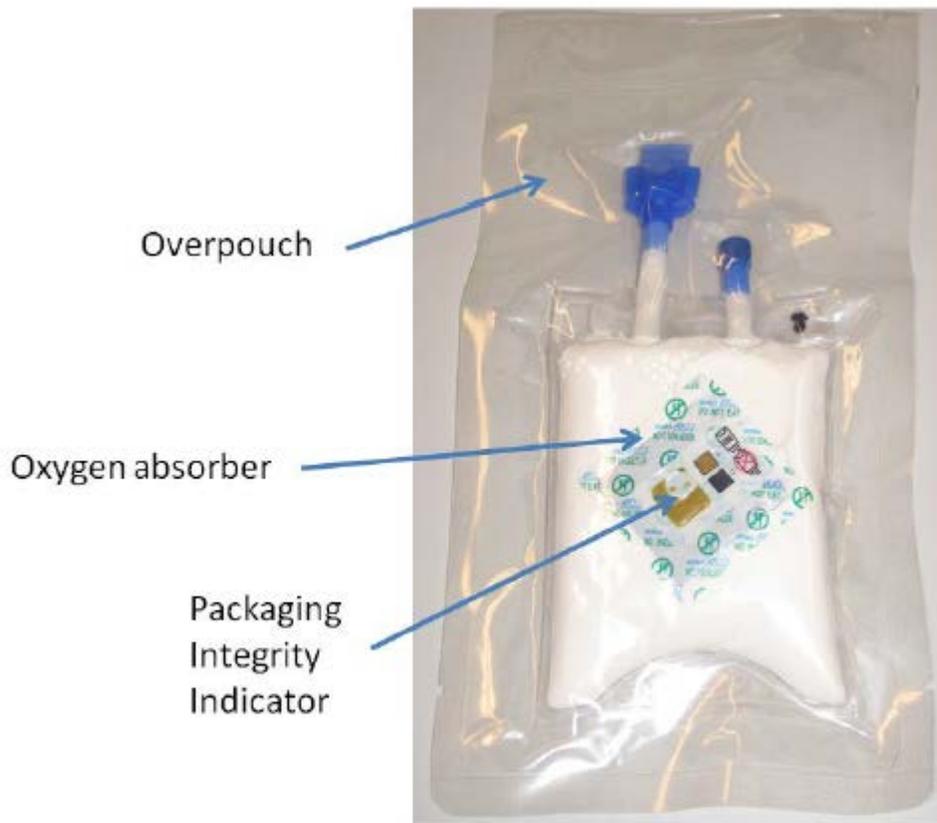
(b) (4)

Secondary Packaging – The Oxygen Absorber & Packaging Integrity Indicator

The oxygen absorber is a sachet (b) (4) containing an oxygen absorbing mixture composed primarily from (b) (4). The mixture is packed in a sachet made from (b) (4). The aim of the oxygen absorber is to absorb the small amount of oxygen ingress that occurs during the shelf life of the drug product.

The packaging integrity indicator (b) (4) consists of a label attached to the oxygen absorber sachet and contains an oxygen indicating mixture based on (b) (4). The oxygen indicating mixture has a clear change in color between the oxidized form (blue) and the reduced form (yellow). This change of color can be visually observed through the overpouch and is explained on the indicator itself. The indicator instructs the user not to use the product if the color of the oxygen indicating mixture does not correspond to the reference color printed next to the OK symbol on the label. The indicator allows for visual identification of the packaging integrity loss.

The following below illustrates the secondary packaging components for the CLARITY (b) (4) Container:



3. Documents Reviewed

Study Number: 2779-R1-ERD, A. (b) (4) ClinOleic 20%, 1000, 500, 250, and 100 mL Container Sizes: Resistance to temperature stability, pressure and leakage.

4. CDRH Review and Comments

CDRH's review of the device constituent for this combination product consisted of an assessment of the sponsor's response to FDA concerns outlined in the previous consults and/or teleconference relative to this device. Specifically, this review assesses the sponsor's response to conform to ISO 15747 Annex A: A.3 Resistance to Temperature Stability, Pressure, and Leakage.

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

ISO 15747 Annex A: A.3 Resistance to Temperature Stability, Pressure, and Leakage

The sponsor has provided testing per ISO 15747 Annex A: A.3 Resistance to Temperature Stability, Pressure, and Leakage in Final Report 2708-RF-ERD, A (Addendum E.16).

Reviewer Assessment: The product is labeled "protect from freezing", therefore (b) (4) was omitted per the ISO 15747 standard. This is considered acceptable.

The sponsor stored 120 test articles in the required temperature and for the duration of time per the ISO standard. The test samples were removed from the calibrated temperature chamber and allowed to go back to room temperature (20°C – 30°C). Each sample was then inserted into a pressure cuff. The cuff was inflated to 50 kPa, and a calibrated pressure station was used for pressure cuff inflating to ensure an accurate pressure value in each cuff. The pressure was maintained for 15 minutes per the ISO standard. The samples were then removed from the pressure cuff and visually inspected to record any leakage. The sponsor states that no leaks were observed in any of the 120 tested articles. This is considered acceptable, and it appears that the sponsor demonstrated that the device passed the physical testing standard in ISO 15747 Annex A: A.3 Resistance to Temperature Stability, Pressure, and Leakage.

5. CDRH Recommendation

Based on the review of the information provided by the sponsor, it appears that Baxter has provided adequate testing methods and results per ISO 15747 Annex A, relative to CDRH's concerns. This included Test A.3: Resistance to Temperature Stability, Pressure, and Leakage, which was the physical test that was missing from the sponsor's previous response. Based on the review, the proposed device appears to be acceptable with respect to device performance testing.

If you have any questions, please contact Jason To at (301) 796 - 6297.

Sincerely,

Jason To -S

Digitally signed by Jason To -S
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ou=FDA, ou=People, cn=Jason To -S,
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Date: 2013.07.31 15:08:31 -04'00'

Jason To
Biomedical Engineer

Concurred By:



Richard C. Chapman
2013.07.31 15:16:04
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Richard Chapman
Chief, General Hospital Devices Branch

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/s/

MATTHEW B BRANCAZIO

08/01/2013

Administratively checked into DARRTS for CDRH reviewer Jason To.



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

Date: June 10, 2013

From: Jason To, Biomedical Engineer
CDRH/ODE/DAGRID/GHDB

To: Matt Brancazio
CDER/OND/ODEIII/DGIEP

Subject: CDRH Consult, GEN1300143/S001, NDA 204508,
(DMF (b) (4) – Type III, CLARITY Container Closure System)

Mary Beth Esche, Associate Director – Global Regulatory Affairs
Baxter Healthcare Corporation
32650 North Wilson Road
Round Lake, IL 60073
Mailstop WG2-3S

Telephone: (224)270-4100
Fax: (224) 270-4119
Email: mary_beth_esche@baxter.com

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 204508. The device constituent of this combination product is the CLARITY container closure system, which consists of a (b) (4) Container configuration. Baxter has provided a response to initial deficiencies as well as additional information and testing per ISO 15747 requested by FDA in a teleconference on May 20, 2013.

2. Device Description

CLARITY (b) (4) Container Packaging Components

(b) (4)



(b) (4)



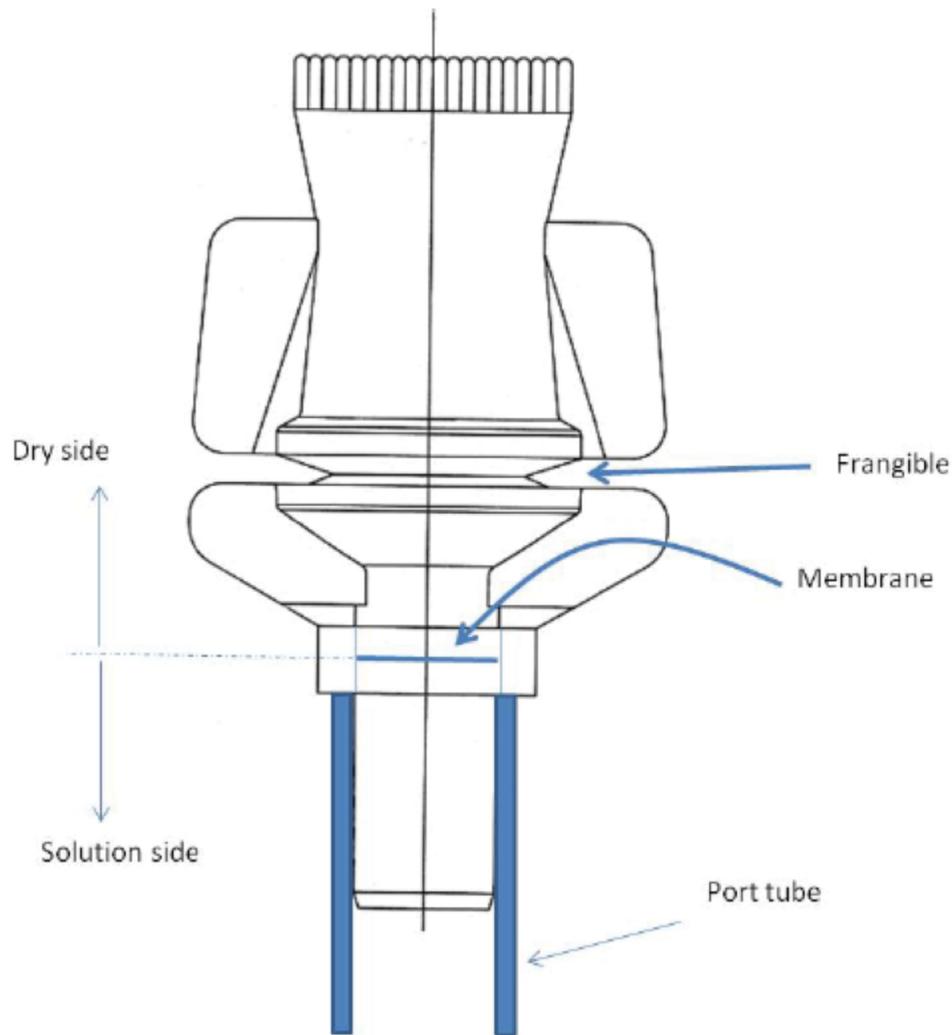
The following figure below illustrates the CLARITY Container: (b) (4)



(b) (4)

Twist-Off Protector Closure

The administration port of the CLARITY (b) (4) Container is closed with a twist-off protector (TOP). This type of closure is (b) (4). The following below illustrates the TOP closure:



Injection Site

The injection site closure is used to close the injection/medication port tube of the CLARITY (b) (4) Container. The injection site allows for (b) (4).

(b) (4)
The

following below is a diagram of the injection site closure:



Secondary Packaging – Clear Overpouch

The secondary packaging is an (b) (4) clear overpouch. The (b) (4) clear overpouch consists of the following:

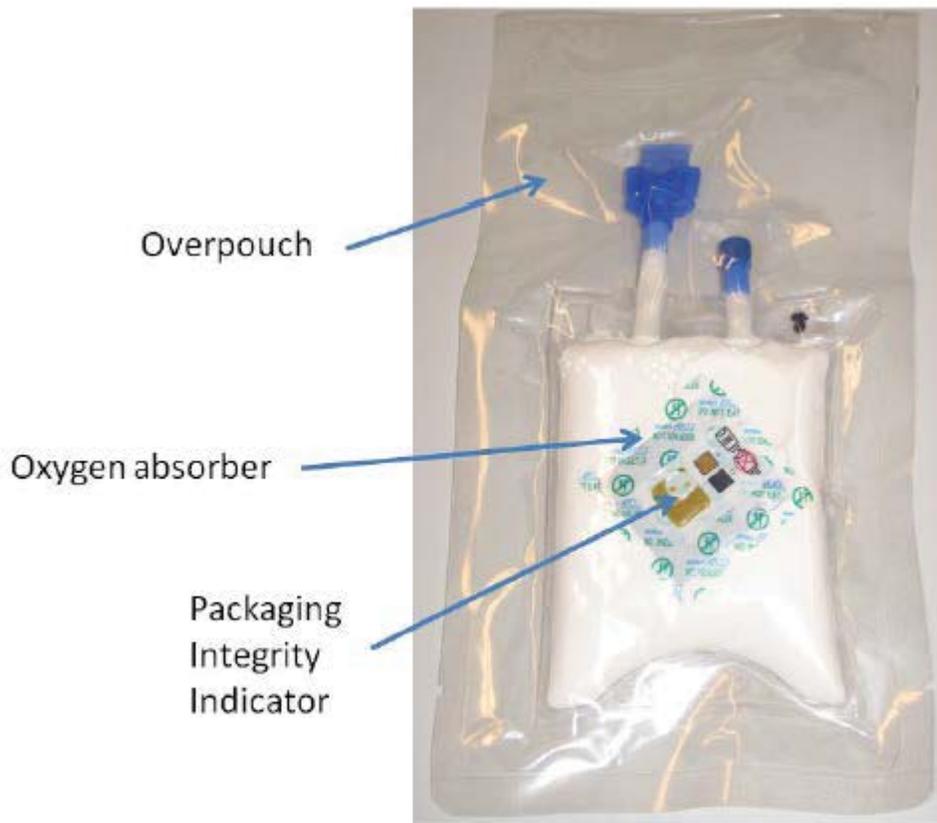


Secondary Packaging – The Oxygen Absorber & Packaging Integrity Indicator

The oxygen absorber is a sachet (b) (4) containing an oxygen absorbing mixture composed primarily from (b) (4). The mixture is packed in a sachet made from (b) (4). The aim of the oxygen absorber is to absorb the small amount of oxygen ingress that occurs during the shelf life of the drug product.

The packaging integrity indicator (b) (4) consists of a label attached to the oxygen absorber sachet and contains an oxygen indicating mixture based (b) (4). The oxygen indicating mixture has a clear change in color between the oxidized form (blue) and the reduced form (yellow). This change of color can be visually observed through the overpouch and is explained on the indicator itself. The indicator instructs the user not to use the product if the color of the oxygen indicating mixture does not correspond to the reference color printed next to the OK symbol on the label. The indicator allows for visual identification of the packaging integrity loss.

The following below illustrates the secondary packaging components for the CLARITY (b) (4) Container:



3. Documents Reviewed

20 MAY 2013 FDA/Baxter Teleconference – ISO 15747, Annex A Testing Request: Amendment. Original/Quality/Physical Testing Information

4. CDRH Review and Comments

CDRH's review of the device constituent for this combination product consisted of an assessment of the sponsor's response to FDA concerns outlined in the initial consult and/or teleconference.

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

Reviewer Comment: The sponsor has agreed to provide additional information and testing per ISO 15747 Annex A: Physical Tests according to FDA's request. The following review will assess the sponsor's conformance to this ISO standard.

CDRH's review will consist of the response's response to the following:

- 1) A.1 General
- 2) A.2 Sampling
- 3) A.3 Resistance to Temperature Stability, Pressure, and Leakage
- 4) A.4 Resistance to Dropping
- 5) A.10 Tightness of the Injection Point
- 6) A.11 Hanger

Review of A.5 Transparency, A.6 Water Vapor Permeability, A.7 Particulate Contamination, A.8 Penetration Ability, A.9 Adhesion Strength of the Infusion Device and Impermeability of the Insertion Point, and A.12 Identification are deferred to CDER. These tests may or may not have been already been addressed in the NDA.

1) A.1 General

The sponsor states that all testing described in A.1 of ISO 15747 were performed using the 1 L CLARITY (b) (4) Containers filled to the nominal capacity of 1 L with lipid emulsion or with water when applicable. All containers were manufactured in the commercial manufacturing facility and (b) (4) before testing.

Reviewer Assessment: This appears to be acceptable.

2) A.2 Sampling

The sponsor has described sampling sizes in the respective test descriptions.

Reviewer Assessment: This appears to be acceptable.

3) A.3 Resistance to Temperature Stability, Pressure, and Leakage

The sponsor has stated that they anticipate completion of Annex A.3 testing in approximately 4 weeks (end of June 2013).

Reviewer Assessment: A.3 testing is CDRH's primary concern regarding this device's performance testing. The sponsor will need to provide the methods and results of this testing to demonstrate that the device can meet its intended use specifications. Review of this device per ISO 15747 A.3 will be postponed until the sponsor provides this information.

4) A.4 Resistance to Dropping

The sponsor performed this test on a hard, rigid, smooth surface at room temperature. The drop height was 0.75 meters. The sponsor reported no leaks were observed upon visual inspection. The sample size was 118 containers.

Reviewer Assessment: This appears to be acceptable.

5) A.10 Tightness of the Injection Point

The sponsor states that the tightness of the injection point of the 1 L CLARITY (b) (4) Container Closure System conforms to this requirement.

The sponsor states that the injection site test was based on USP <381>, which is a more severe challenge than Annex A. 10. USP requires use of a larger, 21 gauge needle (0.8 mm) and multiple piercings instead of the ISO requirement of only a 23 gauge needle (0.6 mm) and a single piercing. In addition, a higher pressure during immersion (b) (4) kPa vs. 20 kPa) and a longer pressurized test period (50 seconds vs. 15 seconds) are used before inspecting for leaks.

A slight modification from USP <381> is that for a flexible container having a medication port mounted on a flexible tube, verification of self sealing

capacity can be done by simply applying air pressure through the tube after puncturing the medication port.

Test Summary:

The injection site of each container was pierced 10 times with a 21 gauge needle. The injection site was then submerged in water and subjected to a pressure of (b) (4) kPa for 50 seconds. No leaks were observed. The sample size was 10 as specified by USP.

Reviewer Assessment: This appears to be acceptable as the sponsor subjected the device to a more challenging test method than the method described in the ISO standard.

6) A.11 Hanger

The sponsor states that the hanger resistance of the 1 L CLARITY (b) (4) Container closure system conforms to this requirement.

Test Summary: Each container was hung on an IV pole for 24 hours through the hanger hole. The container was then inspected for any fracture, tear, or permanent deformation of the hanger hole. No tear, fracture, or permanent deformation was observed. The hanger hole was then cut from the container and submitted to a tensile test. The hanger hole withstood a tensile load (b) (4) N.

Note: The procedure was slightly modified from Annex A.11 in order to have censored data (numerical results) instead of attribute data (pass/fail) in order to limit the sample size, which was 30.

Reviewer Assessment: This appears to be acceptable as the sponsor subjected the device to a more challenging test method than the method described in the ISO standard.

5. CDRH Recommendation

Based on the review of the information provided by the sponsor, Baxter has provided adequate testing methods and results per ISO 15747 Annex A, relative to CDRH's concerns. However, the sponsor has stated that testing per "A.3 Resistance to Temperature Stability, Pressure, and Leakage" will be completed in 4 weeks, approximately by the end of June 2013. This information will be needed in order for CDRH to complete the device's performance review. The sponsor will need to provide the methods and results of this testing to demonstrate that the device can meet its intended

use specifications. Review of this device per ISO 15747 A.3 will be postponed until the sponsor provides this information.

If you have any questions, please contact Jason To at (301) 796 - 6297.

Sincerely,

Jason To -S

Digitally signed by Jason To -S
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ou=FDA, ou=People, cn=Jason To -S,
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Date: 2013.06.10 10:12:11 -04'00'

Jason To
Biomedical Engineer

Concurred By:



Richard C. Chapman
2013.06.10 11:06:13
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Richard Chapman
Chief, General Hospital Devices Branch

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/s/

MATTHEW B BRANCAZIO

08/01/2013

Administratively checked into DARRTS for CDRH reviewer Jason To.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date	July 11, 2013
Reviewer	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD, MS Division of Medication Error Prevention and Analysis
Associate Director	Scott Dallas, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name & Strength	Clinoleic (Lipid Injectable Emulsion, USP) 20%
Application Type/Number	NDA 204508
Applicant	Baxter Healthcare Corporation
OSE RCM #	2013-286

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container, carton and insert labeling for Clinoleic¹ for areas of vulnerability that could lead to medication errors.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested this review as part of their evaluation of the 505(b)(2) submission for Clinoleic (NDA 204508). The reference listed drug (Intralipid 20%, NDA 018449) was approved in January 1981.

2 PRODUCT INFORMATION

The proposed product differs from the reference listed drug (RLD) in that the proposed product contains both olive oil and soybean oil as a source of triglycerides; whereas the reference listed drug (RLD) contains only soybean oil.

The Applicant provided the following information in their January 24, 2013 submission:

- Description: 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/kg/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 over pouch (secondary packaging) provides protection from oxygen ingress and water loss during long term storage of the drug product.

¹ DMEPA found the proposed proprietary name, (b) (4) unacceptable; Clinolipid is the accepted proprietary name (OSE Review 2013-771 dated June 20, 2013)

3 METHODS AND MATERIALS REVIEWED

This section describes the methods and materials we reviewed to better understand the potential for medication errors with the proposed product.

3.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, we evaluated:

- Clinoleic container labels submitted January 25, 2013 (Appendix A)
- Clinoleic carton labeling submitted January 25, 2013 (Appendix B)
- Clinoleic insert labeling submitted January 25, 2013 (no image)
- Intralipid 20% (NDA 014889) Container Label- submitted in the Annual Report dated September 20, 2012 (covering the period from August 1, 2011 through July 31, 2012) to compare to the proposed label/labeling (Appendix C)
- A prototype of the Clinoleic bag provided by the Applicant on March 7, 2013

3.2 FAERS CASES

We searched FAERS using the criteria in Table 1. We downloaded the retrieved cases, and individually reviewed each case for relevance. We excluded cases that were unrelated to medication errors.

Table 1: FAERS* Search Strategy	
Search Dates	January 1, 2004 through March 14, 2013†
Drug Names	Trade Name: Intralipid
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

*Appendix D provides a description of FAERS

† This review is an update to a previous DMEPA review (OSE Review 03-0135)²

3.3 PREVIOUS REVIEWS

On March 5, 2004, DMEPA reviewed 4 AERS reports of medication errors (all determined to be selection errors due to labeling confusion) involving Intralipid². These reports were submitted to the Agency between Intralipid approval and January 1, 2004.

4 RESULTS AND ASSESSMENT

This section provides our findings from the review of the labels, labeling, and medication error cases in FAERS.

4.1 LABELS AND LABELING REVIEW

Our review of the proposed labels and labeling identified outdated information that can be revised to increase the readability and prominence of important information on the container label, carton labeling, and Full Prescribing Information to promote the safe use of the product. Accordingly, we provided comments to the Division and Applicant for suggested revisions (see Section 5).

Of note, we are recommending a dual expression of strength for this drug product. Traditionally, the percentage strength (e.g., 10 % and 20 %) has been the sole strength expression on the label and labeling for lipid products. The advantages of maintaining this tradition include 1) the healthcare practitioners' (i.e., physicians, nurses, and pharmacists) familiarity with the use of percentages for selecting, prescribing, and administering lipid emulsion products; 2) the percentage sign may help to differentiate between the products (e.g., 10% versus 20%); 3) the reference listed drug refers to 20% in the Dosage and Administration section (e.g., do not exceed 12.5 mL of Intralipid 20% per kg); and 4) to maintain consistency in the strength presentation between Intralipid 20 % and this product.

However, the current standard (for labels and labeling in general) is to include the total drug content in total grams per total volume (e.g., 200 grams/1000 mL) followed by the number of grams per milliliter in accordance with USP General Chapter <1> requirements. This updated version of the strength statement is supported by the current recommendations for dosing and administration of this product which is stated as 'XX grams/kg'. Hence, the pharmacist may refer to the total drug content to calculate the appropriate volume of lipid to add to the admixture and may be less prone to calculation errors and the presence of the percentage sign may confirm their selection of the proper strength. See our recommendations below.

4.2 CHARACTERISTICS OF FAERS CASES

Our search retrieved 16 cases from FAERS. After individually reviewing each case, we included seven cases for further analysis. Nine cases were excluded because they described product complaints or adverse events unrelated to medication errors or Intralipid was used as an antidote to a multi-drug overdose (off label use). The NCC MERP Taxonomy of Medication Errors³ was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter.

Table 2 provides the characteristics of the seven cases. Appendix E lists the seven case numbers. Of note, there was one death attributed to a performance deficit (Intralipid protocol wasn't communicated during shift change) that resulted in the administration of 2000 mL of Intralipid over 4.5 hours instead of the intended 387.5 mL.

Table 2. Reported Characteristics for FAERS Cases Associated With Intralipid and Medication Errors, March 5, 2004 – March 14, 2013 (n=7)	
Source	
United States	4
Foreign	3
Type of Medication Error†	
Wrong Dose	2
-300 mL instead of 250 mL (n=1)	
-2000 mL instead of 387.5 mL (n=1)	
Wrong Rate of Administration (faster than prescribed)	4
-10 times the prescribed rate (n=1)	
-Administration rate confused for another co-administered drug (n=2)	
-Administered over 20 minutes (n=1)	
Wrong Route of Administration	1
-Intra-arterially instead of intravenously (n=1)	
Contributing Factors for the Error	
Pump programming error	1
Unknown or not reported	6
Reported Outcomes†	
Death	1
Hospitalization	1
Life-Threatening	3
Disability	1
Other Serious Event	3

†The numbers may not reflect the total number of cases because a case can contain more than one outcome

5 RECOMMENDATIONS

Based on this review, DMEPA provides the following comments and recommendations:

A. Comments to the Division

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

1. The Mixing and Limitations section (under Dosage and Administration) should be reorganized to improve retrieval of information. See Appendix F for our recommendations.

B. Recommendations for the Applicant

DMEPA recommends the following be implemented prior to the approval of this NDA:

1. Container Label
 - a. Delete all references to the proposed proprietary name, (b) (4) since this name was not accepted by the Agency.
 - b. Given the nursing standard of practice for changing IV tubing every 24 hours and that a patient is not likely to use 1000 mL of intralipid in a 24 hour period, consider adding the following statement: “Do not use beyond 24 hours once opened; discard unused portion after 24 hours.” Locate this statement after the storage statement on the principal display panel.
 - c. Relocate the 20% statement to appear after the established name. After the 20% statement, add the total drug content in total grams per total volume followed by the number of grams per milliliter in accordance with USP General Chapter <1> requirements. For example,

Proprietary Name
(Lipid Injectable Emulsion, USP) 20%
200 grams/1000 mL
(0.2 grams/mL)

- d. Relocate the statement “Intravenous Use Only” to appear just below the total drug content and grams per milliliter.
- e. Delete the following statements from the principal display panel to decrease clutter. These statements already appear in the insert labeling.



2. Carton Labeling

- a. Remove the extraneous numbers (e.g., (b) (4)) which appear just before the proprietary name.
- b. Revise the expression of strength as stated in recommendation B(1)(c)

If you have further questions or need clarifications, please contact Phong (Pete) Do, OSE Project Manager, at 301-796-4795.

6 REFERENCES

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² OSE Review OSE Review # 03-0135. Postmarketing Safety Review – Diprivan (Propofol) and Intralipid, Thomas R. March 5, 2004.

³ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

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

Appendix D. Description of FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Appendix E: FAERS case numbers discussed in this review

6441018	7554961	8954689	8020125
6540229	6718509	5801461	

Appendix F. Mixing Guidelines from Insert Labeling

2.3.1. General Information for Mixing

It is essential that the admixture be prepared using strict aseptic techniques as this nutrient mixture is a good growth medium for microorganisms.

Additives must not be added directly to (b) (4) 20% and in no case should (b) (4) 20% be added to the Total Parenteral Nutrition container first.

2.3.2. Proper Mixing Sequence

The following sequence for mixing must be followed to minimize pH related problems by ensuring that typically acidic Dextrose Injections are not mixed with lipid emulsions alone:

1. Transfer Dextrose Injection to the Total Parenteral Nutrition (b) (4) Admixture Container; (b) (4)
2. Transfer Amino Acid Injection (b) (4)
3. Transfer Lipid Emulsion (b) (4)

(b) (4)

2.3.3. Considerations for Final Product

(b) (4)

(b) (4)

(b) (4) can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion. The admixture should also be examined for particulates. The admixture must be discarded if any of the above is observed.

The prime destabilizers of emulsions are excessive acidity (low pH) and inappropriate electrolyte content. Careful consideration should be given to additions of divalent cations (Ca⁺⁺ and Mg⁺⁺) which have been shown to cause emulsion instability. Amino acid solutions exert a buffering effect protecting the emulsion.

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/s/

DENISE V BAUGH
07/11/2013

LUBNA A MERCHANT
07/11/2013

SCOTT M DALLAS
07/12/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

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

Date: June 10, 2013

From: Jason To, Biomedical Engineer
CDRH/ODE/DAGRID/GHDB

To: Matt Brancazio
CDER/OND/ODEIII/DGIEP

Subject: CDRH Consult, GEN1300143/S001, NDA 204508,
(DMF (b) (4) – Type III, CLARITY Container Closure System)

Mary Beth Esche, Associate Director – Global Regulatory Affairs
Baxter Healthcare Corporation
32650 North Wilson Road
Round Lake, IL 60073
Mailstop WG2-3S

Telephone: (224)270-4100
Fax: (224) 270-4119
Email: mary_beth_esche@baxter.com

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 204508. The device constituent of this combination product is the CLARITY container closure system, which consists of a (b) (4) Container configuration. Baxter has provided a response to initial deficiencies as well as additional information and testing per ISO 15747 requested by FDA in a teleconference on May 20, 2013.

2. Device Description

CLARITY (b) (4) Container Packaging Components



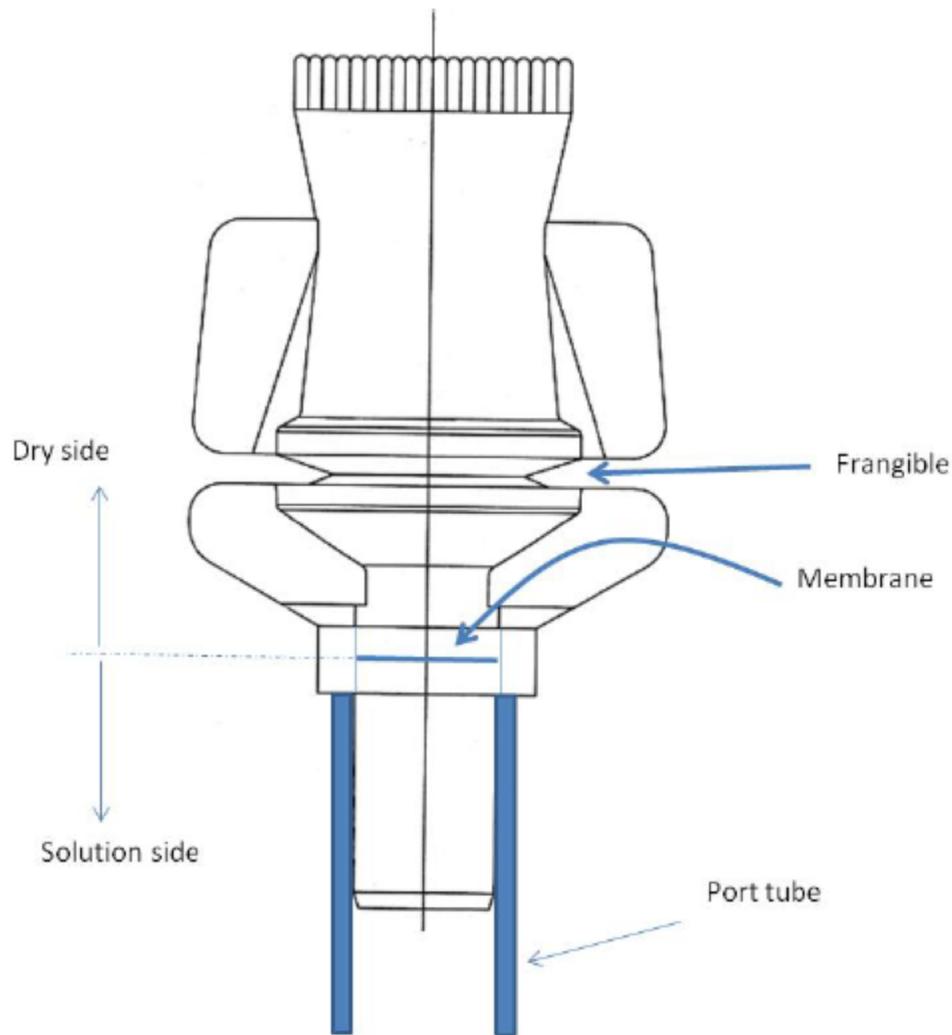
The following figure below illustrates the CLARITY Container: (b) (4)



(b) (4)

Twist-Off Protector Closure

The administration port of the CLARITY (b) (4) Container is closed with a twist-off protector (TOP). This type of closure is (b) (4). The following below illustrates the TOP closure:



Injection Site

The injection site closure is used to close the injection/medication port tube of the CLARITY (b) (4) Container. The injection site allows for (b) (4).

(b) (4) (b) (4)
The

following below is a diagram of the injection site closure:



Secondary Packaging – Clear Overpouch

The secondary packaging is an (b) (4), (b) (4) clear overpouch. The (b) (4) clear overpouch consists of the following:

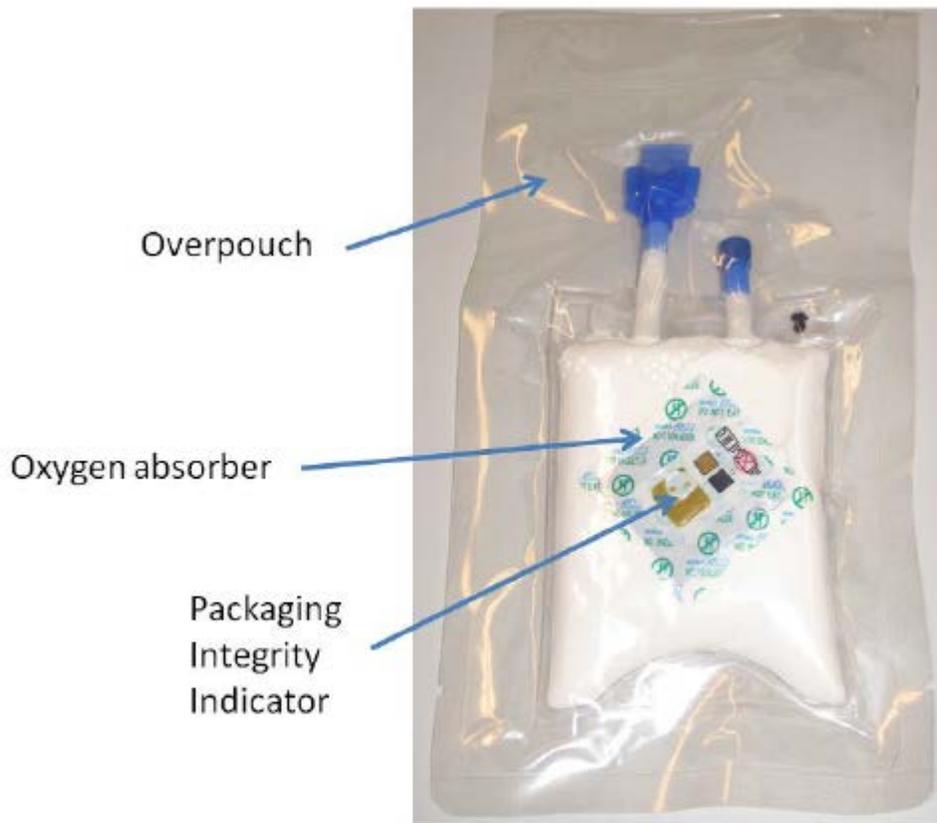


Secondary Packaging – The Oxygen Absorber & Packaging Integrity Indicator

The oxygen absorber is a sachet (b) (4) containing an oxygen absorbing mixture composed primarily from (b) (4). The mixture is packed in a sachet made from (b) (4) materials. The aim of the oxygen absorber is to absorb the small amount of oxygen ingress that occurs during the shelf life of the drug product.

The packaging integrity indicator (b) (4) consists of a label attached to the oxygen absorber sachet and contains an oxygen indicating mixture based on an (b) (4). The oxygen indicating mixture has a clear change in color between the oxidized form (blue) and the reduced form (yellow). This change of color can be visually observed through the overpouch and is explained on the indicator itself. The indicator instructs the user not to use the product if the color of the oxygen indicating mixture does not correspond to the reference color printed next to the OK symbol on the label. The indicator allows for visual identification of the packaging integrity loss.

The following below illustrates the secondary packaging components for the CLARITY (b) (4) Container:



3. Documents Reviewed

20 MAY 2013 FDA/Baxter Teleconference – ISO 15747, Annex A Testing Request: Amendment. Original/Quality/Physical Testing Information

4. CDRH Review and Comments

CDRH's review of the device constituent for this combination product consisted of an assessment of the sponsor's response to FDA concerns outlined in the initial consult and/or teleconference.

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

Reviewer Comment: The sponsor has agreed to provide additional information and testing per ISO 15747 Annex A: Physical Tests according to FDA's request. The following review will assess the sponsor's conformance to this ISO standard.

CDRH's review will consist of the response's response to the following:

- 1) A.1 General
- 2) A.2 Sampling
- 3) A.3 Resistance to Temperature Stability, Pressure, and Leakage
- 4) A.4 Resistance to Dropping
- 5) A.10 Tightness of the Injection Point
- 6) A.11 Hanger

Review of A.5 Transparency, A.6 Water Vapor Permeability, A.7 Particulate Contamination, A.8 Penetration Ability, A.9 Adhesion Strength of the Infusion Device and Impermeability of the Insertion Point, and A.12 Identification are deferred to CDER. These tests may or may not have been already been addressed in the NDA.

1) A.1 General

The sponsor states that all testing described in A.1 of ISO 15747 were performed using the 1 L CLARITY (b) (4) Containers filled to the nominal capacity of 1 L with lipid emulsion or with water when applicable. All containers were manufactured in the commercial manufacturing facility and (b) (4) before testing.

Reviewer Assessment: This appears to be acceptable.

2) A.2 Sampling

The sponsor has described sampling sizes in the respective test descriptions.

Reviewer Assessment: This appears to be acceptable.

3) A.3 Resistance to Temperature Stability, Pressure, and Leakage

The sponsor has stated that they anticipate completion of Annex A.3 testing in approximately 4 weeks (end of June 2013).

Reviewer Assessment: A.3 testing is CDRH's primary concern regarding this device's performance testing. The sponsor will need to provide the methods and results of this testing to demonstrate that the device can meet its intended use specifications. Review of this device per ISO 15747 A.3 will be postponed until the sponsor provides this information.

4) A.4 Resistance to Dropping

The sponsor performed this test on a hard, rigid, smooth surface at room temperature. The drop height was 0.75 meters. The sponsor reported no leaks were observed upon visual inspection. The sample size was 118 containers.

Reviewer Assessment: This appears to be acceptable.

5) A.10 Tightness of the Injection Point

The sponsor states that the tightness of the injection point of the 1 L CLARITY (b) (4) Container Closure System conforms to this requirement.

The sponsor states that the injection site test was based on USP <381>, which is a more severe challenge than Annex A. 10. USP requires use of a larger, 21 gauge needle (0.8 mm) and multiple piercings instead of the ISO requirement of only a 23 gauge needle (0.6 mm) and a single piercing. In addition, a higher pressure during immersion ((b) (4) kPa vs. 20 kPa) and a longer pressurized test period (50 seconds vs. 15 seconds) are used before inspecting for leaks.

A slight modification from USP <381> is that for a flexible container having a medication port mounted on a flexible tube, verification of self sealing

capacity can be done by simply applying air pressure through the tube after puncturing the medication port.

Test Summary:

The injection site of each container was pierced 10 times with a 21 gauge needle. The injection site was then submerged in water and subjected to a pressure of (b) (4) kPa for 50 seconds. No leaks were observed. The sample size was 10 as specified by USP.

Reviewer Assessment: This appears to be acceptable as the sponsor subjected the device to a more challenging test method than the method described in the ISO standard.

6) A.11 Hanger

The sponsor states that the hanger resistance of the 1 L CLARITY (b) (4) Container closure system conforms to this requirement.

Test Summary: Each container was hung on an IV pole for 24 hours through the hanger hole. The container was then inspected for any fracture, tear, or permanent deformation of the hanger hole. No tear, fracture, or permanent deformation was observed. The hanger hole was then cut from the container and submitted to a tensile test. The hanger hole withstood a tensile load (b) (4) N.

Note: The procedure was slightly modified from Annex A.11 in order to have censored data (numerical results) instead of attribute data (pass/fail) in order to limit the sample size, which was 30.

Reviewer Assessment: This appears to be acceptable as the sponsor subjected the device to a more challenging test method than the method described in the ISO standard.

5. CDRH Recommendation

Based on the review of the information provided by the sponsor, Baxter has provided adequate testing methods and results per ISO 15747 Annex A, relative to CDRH's concerns. However, the sponsor has stated that testing per "A.3 Resistance to Temperature Stability, Pressure, and Leakage" will be completed in 4 weeks, approximately by the end of June 2013. This information will be needed in order for CDRH to complete the device's performance review. The sponsor will need to provide the methods and results of this testing to demonstrate that the device can meet its intended

use specifications. Review of this device per ISO 15747 A.3 will be postponed until the sponsor provides this information.

If you have any questions, please contact Jason To at (301) 796 - 6297.

Sincerely,

Jason To
Biomedical Engineer

Concurred By:

Richard Chapman
Chief, General Hospital Devices Branch

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/s/

MATTHEW B BRANCAZIO

06/10/2013

Administratively checked into DARRTS by Project Manager for reviewer.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

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

Date: March 5, 2012

From: Jason To, Biomedical Engineer
CDRH/ODE/DAGRID/GHDB

To: Matt Brancazio
CDER/OND/ODEIII/DGIEP

Subject: CDRH Consult, GEN1300143, NDA 204508,
(DMF (b) (4) – Type III, CLARITY Container Closure System)

Mary Beth Esche, Associate Director – Global Regulatory Affairs
Baxter Healthcare Corporation
32650 North Wilson Road
Round Lake, IL 60073
Mailstop WG2-3S

Telephone: (224)270-4100
Fax: (224) 270-4119
Email: mary_beth_esche@baxter.com

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 204508. The device constituent of this combination product is the CLARITY container closure system, which consists of a (b) (4) Container configuration.

2. Device Description

CLARITY (b) (4) Container Packaging Components

(b) (4)



(b) (4)

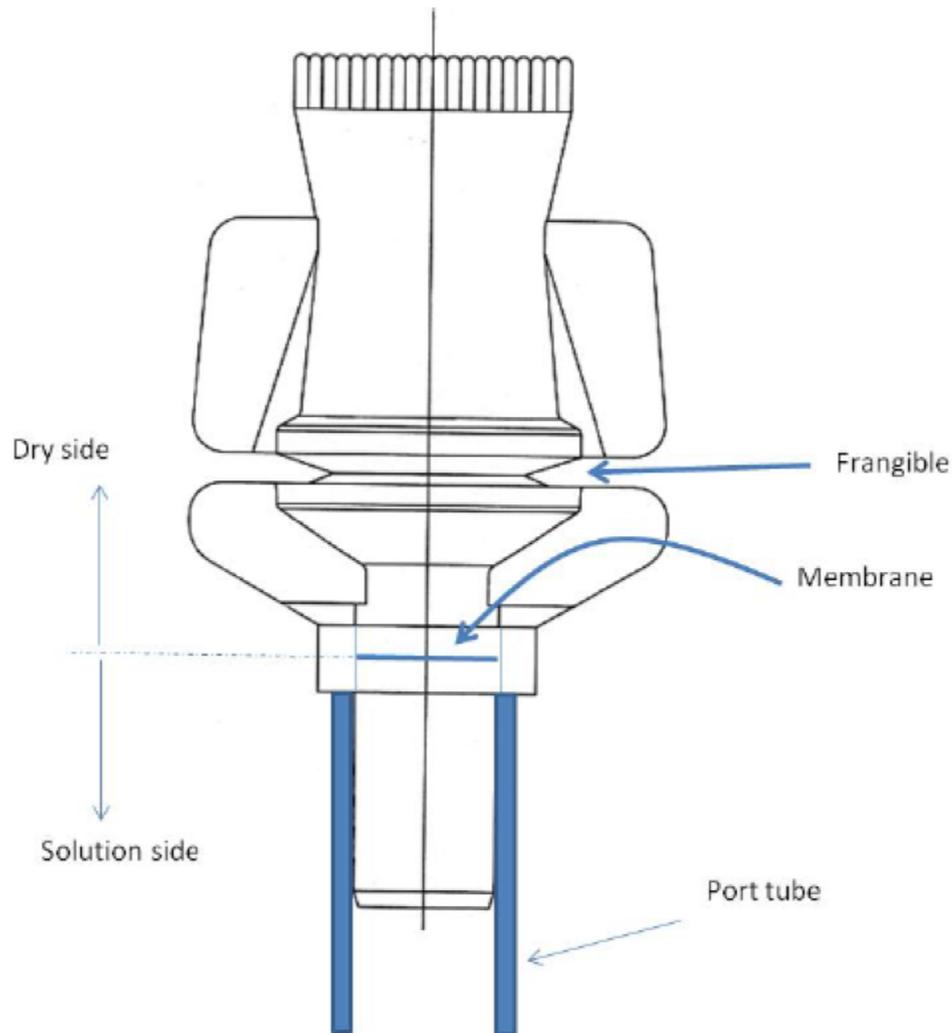


The following figure below illustrates the CLARITY Container: (b) (4)



Twist-Off Protector Closure

The administration port of the CLARITY (b) (4) Container is closed with a twist-off protector (TOP). This type of closure is (b) (4) (b) (4) used to form the TOP closure. The following below illustrates the TOP closure:



Injection Site

The injection site closure is used to close the injection/medication port tube of the CLARITY (b) (4) Container. The injection site allows for (b) (4)

(b) (4)
The

following below is a diagram of the injection site closure:



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The secondary packaging is an (b) (4), (b) (4) clear overpouch. The (b) (4) clear overpouch consists of the following:



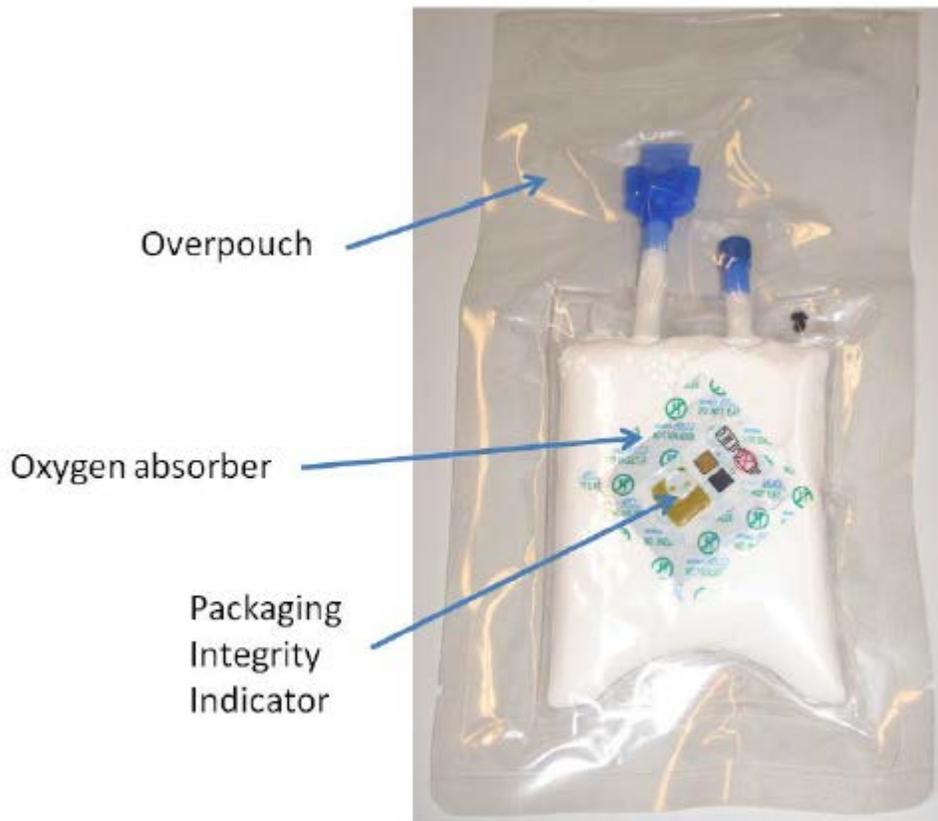
Secondary Packaging – The Oxygen Absorber & Packaging Integrity Indicator

The oxygen absorber is a sachet (b) (4) containing an oxygen absorbing mixture composed primarily from (b) (4). The mixture is packed in a sachet made from (b) (4). The aim of the oxygen absorber is to absorb the small amount of oxygen ingress that occurs during the shelf life of the drug product.

The packaging integrity indicator (b) (4) consists of a label attached to the oxygen absorber sachet and contains an oxygen indicating

mixture based on (b) (4) The oxygen indicating mixture has a clear change in color between the oxidized form (blue) and the reduced form (yellow). This change of color can be visually observed through the overpouch and is explained on the indicator itself. The indicator instructs the user not to use the product if the color of the oxygen indicating mixture does not correspond to the reference color printed next to the OK symbol on the label. The indicator allows for visual identification of the packaging integrity loss.

The following below illustrates the secondary packaging components for the CLARITY (b) (4) Container:



3. Documents Reviewed

DMF (b) (4)

4. CDRH Review and Comments

CDRH's review of the device constituent for this combination product consisted of an assessment of device performance.

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

Reviewer Comment: The sponsor has stated that the performance of the container closure system refers to its ability to function in the manner for which it was designed. The CLARITY (b) (4) Container closure system is designed to protect and contain the sterile dosage form.

The sponsor states the following:

- 1) The performance and functionality of the CLARITY (b) (4) Container closure system are discussed in Section E.4.2. (pages 29-30) of DMF (b) (4).
- 2) Additionally, applicable performance information including results of stability/sterility testing (NDA 204508, Module 3, Section 3.2.P.8.3, pages 1-2, including Tables 1-6) is provided to demonstrate the dosage form is protected by the CLARITY container closure system.
- 3) Container/closure integrity testing in Section G.1.5 and G.1.7.2 (b) (4) (pages 37-40 and 42) also demonstrates that the CLARITY container closure system is an effective barrier to microbial ingress.

The review of the auto-injector device will consist of the evaluation of the relevant documents listed above as stated and provided by the sponsor.

-
- 1) Submission DMF (b) (4)
Module / Section E.4.2
Volume 1 / Section E Pages 29-30

Performance and Functionality: CLARITY (b) (4) Container

The sponsor states that the administration sites (Twist-Off Protector, TOP) and injection sites are tamper evident by design. (b) (4)

(b) (4). As a result, it is clear to the user that an intact Twist-Off Protector is evidence that the sterility of the port is not compromised.

The sponsor states that the injection site of the single chamber container was tested according to functional tests of USP monograph <381>: penetrability, fragmentation, and self-sealing capacity. The results of the testing are summarized below:



Reviewer Assessment: The functional tests performed on the injection site of the device were conducted per USP monograph <381>: penetrability, fragmentation, and self-sealing capacity. However, it appears that this standard has not been reviewed and recognized. Therefore, it is unclear as to whether or not the sponsor has adequately addressed concerns regarding the safety and effectiveness of the device. Furthermore, the sponsor has provided that all testing resulted in a “pass” evaluation. It is unclear as to what procedures, conditions, and parameters the sponsor has utilized in order to perform these tests. The following deficiencies should be conveyed to the sponsor:

- 1) You have provided the results of the functional testing performed on the injection site of the device according to USP monograph <381>: penetrability, fragmentation, and self-sealing capacity. However, it is unclear as to whether you have adequately addressed concerns regarding the safety and effectiveness of the device. Please address the following:
 - a. 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. It is important to demonstrate the worst case scenario which the device may be exposed to during actual use.
 - b. Provide reports for these tests per USP monograph <381>: penetrability, fragmentation, and self-sealing capacity. Ensure that your response outlines the procedures, conditions, and parameters which the device was

subjected to, and explain how this testing demonstrate 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. in order to assure the safety and effectiveness of the device in a worst case scenario.

-
- 2) Submission NDA 204508
Module 3, Section 3.2.P.8.3
Pages 1-2, including Table 1-6

Reviewer Comment: This section is not applicable, as it does not pertain to CDRH.

-
- 3) Submission DMF (b) (4)
Module / Section G.1.5. and G.1.7.2.
Volume 2 / Section G Pages 37-40 and 42

Reviewer Comment: This section is not applicable, as it does not pertain to CDRH.

5. CDRH Recommendation

Based on the review of the information provided by the sponsor, the following questions and concerns should be conveyed to the firm:

Device Performance

- 1) You have provided the results of the functional testing performed on the injection site of the device according to USP monograph <381>: penetrability, fragmentation, and self-sealing capacity. However, it is unclear as to whether you have adequately addressed concerns regarding the safety and effectiveness of the device. Please address the following:
 - a. 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. It is important to demonstrate the worst case scenario which the device may be exposed to during actual use.

- b. Provide reports for these tests per USP monograph <381>: penetrability, fragmentation, and self-sealing capacity. Ensure that your response outlines the procedures, conditions, and parameters which the device was subjected to, and explain how this testing demonstrate 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. in order to assure the safety and effectiveness of the device in a worst case scenario.

If you have any questions, please contact Jason To at (301) 796 - 6297.

Sincerely,

Digitally signed by Jason To -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Jason To -S,
0.9.2342.19200300.100.1.1=2000489354
Date: 2013.04.22 13:55:06 -04'00'

Jason To -S

Jason To
Biomedical Engineer

Concurred By:

Digitally signed by Jacqueline S. Ryan
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200057029
3, cn=Jacqueline S. Ryan
Date: 2013.04.22 14:01:42 -04'00'

Jacqueline S. Ryan

Jacqueline Ryan
Combination Product Team Leader

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

/s/

MATTHEW B BRANCAZIO

05/20/2013

Administratively signing for Jason To, Biomedical Engineer CDRH/ODE/DAGRID/GHDB.

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information	
NDA # 204508	
Proprietary Name: ClinOleic 20% Established/Proper Name: 20% Lipid Injectable Emulsion, USP Dosage Form: Intravenous emulsion Strengths: 20%	
Applicant: Baxter Healthcare Corp Agent for Applicant (if applicable):	
Date of Application: January 3, 2013 Date of Receipt: January 3, 2013 Date clock started after UN: N/A	
PDUFA Goal Date: July 3, 2013	Action Goal Date (if different): July 3, 2013
Filing Date: March 4, 2013	Date of Filing Meeting: January 30, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5	
Proposed indication(s)/Proposed change(s): parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced NDA Number(s): Intralipid 20% NDA 18499				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	x			Priority
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> If yes, explain in comment column.		X		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:		x		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

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

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

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

(BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #			X	
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
• If yes, were all of them submitted on time?			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?		X		
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	x			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			x	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			x	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		x		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			x	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			x	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>			x	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		x		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	x			
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>		x		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

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

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

	<input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	x			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	x			
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/11/13	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 30, 2013

BLA/NDA/Supp #: 204508

PROPRIETARY NAME: ClinOleic 20%

ESTABLISHED/PROPER NAME: 20% Lipid Emulsion, USP

DOSAGE FORM/STRENGTH: 20% lipid emulsion (intravenous)

APPLICANT: Baxter Healthcare Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Parenteral Nutrition

BACKGROUND: Baxter Healthcare Corporation submitted NDA 204508 on January 3, 2013. ClinOleic 20% is a lipid emulsion indicated for parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated. NDA 204508 is relying upon product NDA 18499 Intralipid 20% (from Fresenius) as the RLD. Baxter is currently the distributor of Intralipid 20% and asks for an expedited review because of the lipid emulsion shortage in the U.S. market.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matt Brancazio	Y
	CPMS/TL:	Wes Ishihara	Y
Cross-Discipline Team Leader (CDTL)	Rob Fiorentino		Y
Clinical	Reviewer:	Klaus Gottlieb	Y
	TL:	Rob Fiorentino	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Denise Miller	N
	TL:		

Clinical Pharmacology	Reviewer:	Kris Estes	Y
	TL:	Sue-Chih Lee	N
Biostatistics	Reviewer:	Mike Welch	Y
	TL:	Behrang Vali	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dinesh Gautum	Y
	TL:	Sushanta Chakdar	Y
Product Quality (CMC)	Reviewer:	Tarun Mehta	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Kassa Ayalew	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kendra Worthy	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	Yasmin Choudhry	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
OPDP	Reviewer	Kathleen Klemm	
		Kendra Jones	
Compliance officer/facility reviewer	Reviewer	Rokhsana Safaai-Jazi	
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		

	TL:		
Other reviewers			
Other attendees	Joyce Korvick, Donna Griebel, Andrew Mulberg		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: no comments</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIostatISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

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

REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Donna Griebel, M.D.</p> <p>4/3/13</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) <p>notify OMPQ (so facility inspections can be scheduled earlier)</p>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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/s/

MATTHEW B BRANCAZIO
03/04/2013

RICHARD W ISHIHARA
03/04/2013