



NDA 217382

**COMPLETE RESPONSE**

ResQ Pharma  
c/o Brij Strategic Consultations, LLC  
610 Professional Dr., Suite 103  
Gaithersburg, MD 20879

Attention: Mukesh Kumar, PhD  
Sponsor's Authorized Representative

Dear Dr. Kumar:

Please refer to your new drug application ( (b) (4) )  
(b) (4) for (b) (4) (20% soybean oil emulsion), for intravenous infusion.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**CLINICAL AND BIOPHARMACEUTICS**

**Deficiency 1**

You are relying on published literature submitted in your NDA on lipid emulsion therapy for the treatment of local anesthetic systemic toxicity (LAST), most of which describes the use of Intralipid 20% (NDA 018449) or does not specify which lipid formulation is used in the study. Your application cross-references Nutrilipid 20% (NDA 019531); however, you have not identified any published reports citing the administration of Nutrilipid 20% for treatment of LAST. Given the absence of data for Nutrilipid 20% and paucity of data for other lipid emulsions (excluding Intralipid 20%), we are unable to determine whether Nutrilipid 20% is safe and effective for the treatment of LAST.

We acknowledge that Nutrilipid 20% and Intralipid 20% have an AP therapeutic equivalence rating in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) and note that you state that bioequivalence is self-evident under the criteria described in 21 CFR Part 320.22(b)(1) despite the fact that your product is an emulsion (not a solution) and differs in inactive ingredients and/or concentration of inactive ingredients (see Table 1 below).<sup>1</sup>

**Table 1. Composition comparison of Nutrilipid 20% and Intralipid 20%**

Composition	Nutrilipid 20% (b) (4)	Intralipid 20%
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Furthermore, you argue that physicochemical comparison between Nutrilipid 20% and Intralipid 20% support a conclusion of comparable surface area to support an expectation of comparable efficacy between the two products. We also acknowledge that you have performed comparative testing for physicochemical properties for Nutrilipid 20% and Intralipid 20% to establish a scientific bridge and justify reliance on the published literature using Intralipid 20% for the treatment of LAST. However, the results of the physicochemical comparison indicate that there are statistically significant differences in zeta potential, viscosity, osmolality, and pH between Nutrilipid 20% and Intralipid 20%. Additionally, your application does not contain adequate information and justification as to whether those differences would affect the in vivo performance of your drug product for use in the treatment of LAST.

Therefore, we have determined that your submissions and rationale are not adequate to establish a scientific bridge between Nutrilipid 20% and Intralipid 20% to rely on the published literature describing the treatment of LAST with Intralipid 20%.

In addition, given that Nutrilipid 20% and Intralipid 20% differ qualitatively and quantitatively in formulation composition, additional data are needed to demonstrate that Nutrilipid 20% and Intralipid 20% have comparable drug capture capability to support that the published literature describing the treatment of LAST with Intralipid 20% is scientifically relevant to your proposed product for the proposed use.

Information needed to resolve Deficiency 1

Provide additional data that demonstrate that Nutrilipid 20% and Intralipid 20% have the comparable drug capture capability to establish the bridge between the two products for the proposed indication. You should also provide justification as to why the physicochemical differences between Nutrilipid 20% and Intralipid 20% do not affect the in vivo performance of your drug product for use in the treatment of LAST. Lastly, provide justification to support the applicability of any safety and effectiveness data available in published literature regarding different lipid formulations (i.e., not Intralipid) and different concentrations of Intralipid (i.e., not 20%) to your drug product.

Provide, in your clinical summaries, detailed information regarding your published literature search strategy and methods. Specifically, provide details including the following:

1. Databases evaluated, specific search string(s) used, search terms, fields searched (e.g., title, key words, full text), specific search dates, and any inclusion or exclusion criteria. Indicate if the search strategy utilized differed with regard to case reports versus other type of published studies. Also indicate if the search strategy differed with regard to literature data needed to support efficacy versus safety.
2. Justification for the search strategy and dates chosen.
3. Justification on how you determined what literature references to ultimately include and which to exclude in your safety and efficacy assessment, and your rationale as to how you made these determinations. Exclusion of any literature references where lipid emulsion was not demonstrated to be efficacious should be justified.
4. Methods used to evaluate for duplication of case reports particularly those that were included as part of published case series.

## **NONCLINICAL**

(b) (4)

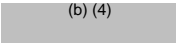



(b) (4)



## **HUMAN FACTORS**

### **Deficiency 4**

The results of your human factors (HF) validation study for your proposed  (b) (4)  demonstrated several use errors and use difficulties with critical tasks that indicate the proposed user interface does not support safe and effective use by the intended users and for intended use in the intended use environment. Based on the subjective feedback and root cause analyses from the HF validation study, we determine that you will need to develop and implement additional risk controls, including risk controls that consider both device design and relevant labels and labeling, in order to address the identified use issues and reduce the risk of associated medication errors. For example,

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the root cause analyses and subjective feedback for many of the use issues for critical tasks pointed to the participants' previous experiences with infusion pumps, concerns about calculating doses and infusions other than those specified in the Instructions for Use, high cognitive load and unfamiliarity with calculating of drops per second and counting drops in drip chamber during high stress situations, as well as confusion with aspects of the Instructions for Use and LAST Management Flow Process in an emergency use situation. We provide some packaging and labeling recommendations in Table A below.

Information needed to resolve Deficiency 4:

(b) (4)



(b) (4)



(b) (4)



(b) (4)



**PRESCRIBING INFORMATION**

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources<sup>7</sup> and Pregnancy and Lactation Labeling Final Rule<sup>8</sup> websites, including regulations and related guidance documents and the Selected

(b) (4)





Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at [FDA.gov](http://FDA.gov).<sup>9</sup>

## **CARTON AND CONTAINER LABELING**

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)

**PROPRIETARY NAME**

Please refer to correspondence dated (b) (4), which addresses the proposed proprietary names, (b) (4) %. These names were found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary names when you respond to all of the application deficiencies that have been identified in this letter.

**SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug product under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
  - Present tabulations of the new safety data combined with the original application data.
  - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this drug product. Include an updated estimate of use for drug product marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

### **ADDITIONAL COMMENTS**

We have the following comments/recommendations that are not approvability issues:

#### **Product Quality**

(b) (4)

**Regulatory**

2. You submitted a Letter of Authorization (LOA) (b) (4)

[REDACTED]

(b) (4)

[REDACTED]

**Clinical**

3. In your Integrated Summary of Efficacy, you described data from 103 case reports that reported administration of lipid emulsion therapy and 138 case reports that did not report administration of lipid emulsion therapy for the treatment of LAST. Given that your literature search spanned many years and went back as far as 1958, differences in outcome may reflect changes in practice of medicine including, but not limited to, timing of LAST recognition, availability of resuscitation drugs and other supportive therapies, and changes in resuscitation protocols that could ultimately have major impacts on patient outcomes. It appears that more than half of the 138 reports (that did not use lipid emulsion therapy for treatment of LAST) are over 20 years old, whereas the first reported use of lipid emulsion therapy for a patient experiencing LAST was around 2006. Given the challenges with comparing outcome measures using such historical control data, additional justification regarding applicability of such comparisons is necessary. Specifically, provide a justification on the applicability of comparative statements in your Integrated Summary of Efficacy and why you believe your statistical analyses comparing the two groups (those that received lipid emulsion and those that did not) are appropriate. Your justification should take into account dates of the publications and discuss how changes in the practice of medicine over the last 60+ years may have impacted the reported patient outcomes.
4. Final determination on the adequacy of the published literature to support the safety and effectiveness of (b) (4) for the indication of treatment of LAST in adult patients will be deferred until an adequate scientific bridge between Intralipid and Nutrilipid has been established. Our preliminary assessment is that there may be enough data to support the safety and effectiveness of Intralipid in treatment of LAST during cardiac arrest or life-threatening toxicity (e.g., ventricular arrhythmia). However, evidence to support the safety and effectiveness and benefit:risk assessment of Intralipid to treat LAST presenting as non-life-threatening toxicity (e.g., perioral numbness, mild to moderate hypotension) is comparatively limited and additional evidence may be required,



particularly because many mild-moderate signs and symptoms may be transient, self-limiting or resolve with other supportive therapies (i.e., hypotension may respond to fluid or a vasopressor). Therefore, in your resubmission, provide additional data and/or justification to support the benefit:risk of (b) (4) therapy for treatment of non-life-threatening signs and symptoms of LAST. Furthermore, your benefit: risk discussion should take into consideration which local anesthetics you intend to include in your indication statement (refer to comment #6 below).

5. Final determination on the adequacy of the published literature to support the safety and effectiveness of (b) (4) for the indication of treatment of LAST in pediatric patients will be deferred until an adequate scientific bridge between Intralipid and Nutrilipid has been established. Our preliminary assessment is that there may be enough data to support the safety and effectiveness of Intralipid in treatment of LAST during cardiac arrest or life-threatening toxicity (e.g., ventricular arrhythmia) in pediatric patients. However, evidence to support the safety and effectiveness and benefit:risk assessment of Intralipid to treat LAST presenting as non-life-threatening toxicity in pediatric patients is comparatively limited and additional evidence may be required, particularly because many mild-moderate signs and symptoms may be transient, self-limiting or resolve with other supportive therapies. Therefore, in your resubmission, provide additional data and/or justification to support the benefit:risk of (b) (4) for treatment of non-life-threatening signs and symptoms of LAST in pediatric patients of all ages. Furthermore, your benefit:risk discussion should take into consideration which local anesthetics you intend to include in your indication statement (refer to comment #6 below).

We also note that given the paucity of literature references provided that definitively administered Intralipid for the treatment of LAST in pediatric patients, you will need to provide additional justification why the available data are adequate to support all aspects of labeling, including the recommended dosing regimen, in pediatric patients of all age groups. Refer to labeling comment below regarding differences in the proposed (b) (4) labeling and Nutrilipid 20% labeling.

6. Your proposed prescribing information was not fully reviewed during this review cycle due to the Complete Response action. However, there appear to be some discrepancies in your NDA submission regarding the proposed indication. Specifically, the proposed prescribing information for (b) (4) lists the following indication: (b) (4) 20%, a soybean oil emulsion indicated as a treatment for local anesthetic systemic toxicity (LAST). In contrast, in the Clinical Overview document you state, “(b) (4) it is intended as an adjunctive treatment of local anesthetic systemic toxicity (LAST). LAST related to the following local anesthetic agents is considered treatable with (b) (4) : Amides: Bupivacaine, Levobupivacaine, Lidocaine, Mepivacaine, Prilocaine,

Ropivacaine, Etidocaine, and Articaine; and Esters: Procaine, Chlorprocaine, Tetracaine and Cocaine." Furthermore, in the Integrated Summary of Efficacy document, you state, "We will limit the local anesthetics for which we seek approval of the (b) (4) kit label for treating local anesthetic systemic toxicity (LAST) specifically to lidocaine, bupivacaine/levobupivacaine, and ropivacaine alone or in combination with each other. Bupivacaine/levobupivacaine (the racemic mixture and levorotatory enantiomer, respectively) can be considered chemically equivalent for the purposes of this discussion. These local anesthetics were selected based on their chemical characteristics, the known mechanisms of lipid resuscitation, and their clinical relevance as shown in a database of published cases [of] LAST." In your NDA resubmission, clarify what indication you are seeking, and specifically, whether you intend to limit the indication to treatment of LAST resulting from certain local anesthetics versus treatment of LAST resulting from any local anesthetic. Include an evidenced-based justification for the indication you propose.

7. Based on the proposed dosing regimen and the maximum total dose of (b) (4) of 10 ml/kg, a patient could receive (b) (4) treatment (bolus + infusion) for 34 minutes prior to reaching the maximum recommended dose. If, however, repeat bolus is required and the infusion rate is doubled (as recommended in your proposed prescribing information) because response is not achieved with the first bolus and infusion, then the maximum treatment duration would be approximately 14 minutes prior to reaching the maximum recommended dose. We note that some case reports submitted described treatment durations that greatly exceeded 34 minutes. In your NDA resubmission, provide recommendations on additional treatment options if the maximum dose of (b) (4) has been administered with no effect. These recommendations should be based on patient clinical condition and what alternatives therapies may be readily available.
8. We note that in 2023, labeling updates were made to Nutrilipid 20% (NDA 019531) prescribing information, including, but not limited to, removal of the boxed warning. In your resubmission, address any differences in the prescribing information, particularly those regarding pediatric patients, including the boxed warning, between your product compared to the current prescribing information for Nutrilipid (NDA 019531) and Intralipid (NDA 018449). Any differences in labeling with regard to safety-related changes will need to be adequately justified. In addition, update your annotated labeling to reflect any labeling changes you propose.

## **Nonclinical**

(b) (4)

(b) (4)

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact

(b) (4)

Sincerely,

*{See appended electronic signature page}*

(b) (4)

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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(b) (4)

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