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RESEARCH**

*APPLICATION NUMBER:*

**021064Orig1s011**

**OTHER ACTION LETTERS**



NDA 21-064/S-11

**COMPLETE RESPONSE**

Lantheus Medical Imaging Inc.  
Attention: Nancy Blair  
Associate Director, Regulatory Affairs  
331 Treble Cove Road  
North Billerica, MA 01862

Dear Ms. Blair:

Please refer to your Supplemental New Drug Application (sNDA) dated September 29, 2010, received September 29, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Definity (Perflutren Lipid Microsphere).

We acknowledge receipt of your amendments dated November 23 and December 16, 2010, January 19, February 18, February 24, April 21, April 27, June 14, June 21, and June 30, 2011.

This "Prior Approval" efficacy supplemental new drug application proposed modification of the prescribing information to add (b) (4) alteration of the safety information, (b) (4)

The proposal also reformatted the prescribing information to maintain consistency with the expectations of the Physician Labeling Rule (PLR).

We have completed the review of your application, as amended, 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**

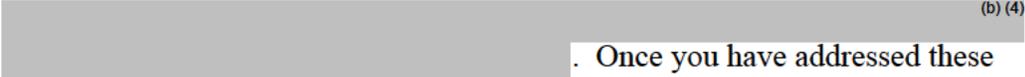
(b) (4)

(b) (4)

To support this claim, we recommend you obtain data from prospective, adequate and well-controlled clinical trials in the appropriate patient population. Listed below are some of the data limitations that exemplify our concerns with the results from these studies.

(b) (4)

3. Regarding the proposed alterations of safety information within the prescribing information:

- a. The supplied information importantly contributes to the assessment of the safety of Definity. This information appears to support some of your proposed changes to the label. However, we do not agree with elimination of the boxed warning. We supplied you with a draft version of potentially acceptable labeling during the review cycle.
- b.  (b) (4). Once you have addressed these concerns, we encourage you to supply revised labeling that either incorporates the edits we have previously supplied or justifies alternative text.
- c. The safety data sources consisted of a pulmonary hemodynamic study (DMP 115-416), a “registry” study (DMP 115-415), an observational study of Definity use among critically ill patients (DMP 115-418), and post-marketing pharmacovigilance data. With the exception of the observational study (DMP 115-418), we regard these data sources as providing summary information appropriate for inclusion within the prescribing information, as illustrated by the draft text we proposed during the review cycle. As discussed at the May 2, 2011 Advisory Committee meeting, the observational study (DMP 115-418) has several important limitations that render the

study conducive to misinterpretation; we do not regard this study's findings as appropriate for inclusion within the prescribing information.

(b) (4)

## **LABELING**

We reserve further comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

## **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 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 the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA 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 patient 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 NDA 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. Include an updated estimate of use for drug marketed in other countries.
  8. Provide English translations of current approved foreign labeling not previously submitted.

### **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 supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

*{See appended electronic signature page}*

Rafel Dwaine Rieves, M.D.  
Director,  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAFEL D RIEVES  
07/28/2011