DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-064/S-009

Lantheus Medical Imaging
Attention: Nancy Blair
Manager, Regulatory Affairs
331 Treble Cove Road
North Billerica, MA 01862

Dear Ms. Blair:

Please refer to your supplemental new drug application dated April 8, 2008, received April 9, 2008, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Definity® (perflutren lipid microsphere) Injectable Suspension.

We acknowledge receipt of your submission dated May 6, 2008.

This supplemental new drug application provides for revision of the Definity label to modify the boxed WARNING, WARNINGS, CONTRAINDICATIONS and ADVERSE REACTIONS: Post Marketing Experience. These modifications clarify the post-administration monitoring plan, remove certain contraindications and update the Warnings.

We completed our review of this supplemental new drug application and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, submitted May 6, 2008).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-064/S-009**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

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

supplemental new drug application (NDA) dated April 8, 2008, is not an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Therefore, there are no new pediatric assessments required in conjunction with this supplemental NDA.

However, pediatric assessments were required in conjunction with your original NDA. In the original approval letter dated July 31, 2001, we deferred submission of your pediatric studies because pediatric studies should be delayed until additional safety or effectiveness data were available in the postmarketing setting in adults before studying children. To date, you have not submitted plans for conducting these required pediatric studies.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act.

Please provide an update, within 90 days, of your plans to conduct these required pediatric postmarketing studies to assess the safety and efficacy of Definity. Submit the update and all clinical protocols to IND 48,626 with a cross-reference letter to this NDA 21-064. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessments**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Since Definity was approved in 2001 for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border, we have become aware of postmarketing reports of serious cardiopulmonary reactions and deaths shortly following Definity administration. This information was not available when Definity was approved. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) will not be sufficient to assess the signals of serious risk of cardiopulmonary adverse reactions in patients with pulmonary hypertension or unstable cardiopulmonary conditions following administration of Definity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess these signals of a serious risk.

Finally, we have determined that an observational study in which patients with defined underlying risk are carefully evaluated following administration of Definity will be useful but not sufficient to assess the signals of serious risk of cardiopulmonary adverse reactions in patients with pulmonary

hypertension or unstable cardiopulmonary conditions. A clinical trial in which baseline and post drug administration pulmonary hemodynamic data are collected is necessary to fully assess this risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the Act, to conduct a study and a clinical trial.

You are required to conduct the following study:

1. A study that will utilize an existing database to compare in-hospital mortality in critically ill patients undergoing echocardiography with and without Definity. Mortality will be compared between patients who receive Definity and patients who do not receive Definity. This study will consist of the development of an analytical protocol which will be submitted for review by the FDA in order to optimize the analytical methodology, including appropriate methods to adjust for imbalances in baseline characteristics and to provide sample size estimation.

The timetable you submitted on April 8, 2008 states that you will conduct this study according to the following timetable:

Draft Protocol Submission:	by July 2008
Final Report Submission:	by November 2009

FDA anticipates completion of the review of the draft protocol analytical plan for the existing database within 30 days following submission of the draft document and supportive information.

In addition, you are required to conduct the following clinical trial:

2. A clinical trial that, at a minimum, provides pulmonary hemodynamic data from at least 30 patients with known or suspected cardiac disease and who are undergoing an echocardiogram with Definity administration. At least 15 of these patients will have pulmonary artery hypertension documented on baseline pulmonary artery pressure assessment. In addition to the collection of any other information, pulmonary artery pressures will be collected at baseline (pre-administration of Definity) and at various time points (e.g., two, five and 10 minutes) post-administration.

The timetable you submitted on April 8, 2008 states that you will conduct this trial according to the following timetable:

Protocol Submission:	by July 2008
Trial Start:	by January 2009
Final Report Submission:	by November 2009

Submit clinical protocols to IND 48,626, with a cross-reference letter to this NDA 21-064. Submit all final reports to your NDA 21-064. Use the following designators to prominently label all submissions, including supplements, relating to these study and clinical trial requirements as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

You are required to report periodically to FDA on the status of this postmarketing study pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.81. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with Definity.
As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA XXX."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" Letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). We also request that you provide an update, within 90 days, of your plans for the development of pediatric studies that assess the safety and efficacy of Definity (21 CFR 314.55). We refer to our letter of July 31, 2001 that noted your pediatric plans were deferred until you had obtained post-approval experience with Definity.

If you have any questions, call Renee Tyson, Regulatory Project Manager, at (301) 796-1476.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Rafel Rieves

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