

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021064Orig1s011

MEDICAL REVIEW(S)

DIVISION OF MEDICAL IMAGING PRODUCTS

Date: October 21, 2011
Sponsor: Lantheus Medical Imaging
Product: Definity
Regulatory submission: NDA 21064
Reviewer: Ross Filice, M.D. DMIP/ODE IV/CDER
Through Libero Marzella, M.D. DMIP/ODEIV/CDER

Background

The sponsor originally submitted an efficacy supplement in 2010 (b) (4), new safety information, (b) (4). A Complete Response letter was issued in July, 2011 noting (b) (4) that the safety (b) (4) information was acceptable. The sponsor withdrew (b) (4) and labeling was agreed on that included the new safety (b) (4)

However, shortly after the CR letter was issued, the Office of Regulatory Policy found that the sponsor inappropriately bundled their submission and that three separate submissions ((b) (4)) with three separate user fees should have been submitted. After discussion with the sponsor, they requested that only the safety information be considered with one corresponding user fee. (b) (4)

In accordance with this plan, the sponsor submitted the agreed upon labeling which includes the new safety information. (b) (4) save for modifications to convert that information to PLR format.

Findings and Regulatory Action

The submitted labeling is exactly the same as the previously agreed upon labeling (b) (4) submitted labeling. The reviewer recommends approval of the submitted labeling.

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/s/

ROSS W FILICE
10/21/2011

LIBERO L MARZELLA
10/24/2011

CLINICAL REVIEW

Application Type sNDA
Application Number(s) 21064
Priority or Standard Standard

Submit Date(s) 9/29/2010
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Reviewer Name(s) Ross Filice, M.D.
Review Completion Date 9/21/2011

Established Name perflutren lipid microsphere
injectable suspension
(Proposed) Trade Name Definity
Therapeutic Class Diagnostic Agent
Applicant Lantheus Medical Imaging,
Inc.

Formulation(s) perflutren microspheres and
octafluoropropane (after
Vialmix activation)
Dosing Regimen **Bolus**: 10 μ L/kg within 30-60
seconds followed by 10mL
saline flush. If necessary, but
only after at least 30 minutes
have elapsed, second 10 μ L/kg

dose and saline flush to prolong enhancement.

Infusion: 1.3mL in 50mL saline initiated at 4.0 mL/min with titration to optimize enhancement, not to exceed 10mL/min

Imaging: Mechanical index of ultrasound device should be 0.8 or less. Enhanced images should be evaluated in combination with non-contrast images.

Indication(s)	Activated DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The safety and efficacy of DEFINITY® with exercise stress or pharmacologic stress testing have not been established.
Intended Population(s)	Patients with suboptimal echocardiograms.

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Division of Medical Imaging Products - Clinical Review

Ross Filice, M.D.

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DEFINITY (perflutren lipid microsphere) injectable suspension

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Abbreviations

µm	micrometer
A2C	apical 2 chamber view
A4C	apical 4 chamber view
AE	adverse event
AERS	Adverse Event Reporting System
AHRQ	Agency for Healthcare Research and Quality
AVI	audio video interleave
BP	blood pressure
BPM	beats per minute
C3a	complement protein C3a
CAD	coronary artery disease
CDM	common data model
DSE	dobutamine stress echocardiography
EBD	Endocardial border delineation
EBL	Endocardial border length
EBLc	Endocardial border length (continuous)
ECG	electrocardiogram
ED	emergency department
EE	Efficacy-evaluable population
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GE	General Electric (Healthcare)
HCUP	Healthcare Cost and Utilization Project (AHRQ)
htn	hypertension
ICL	imaging core laboratory
ICU	intensive care unit
IHCarUS	Inpatient Health Care Utilization System (SDI)
LAD	left anterior descending (coronary artery)
LMI	Lantheus Medical Imaging
LVO	Left ventricular opacification
mmHg	millimeters of mercury
MPI	myocardial perfusion imaging
NDA	New Drug Application
NHDS	National Hospital Discharge Survey
NOS	not otherwise specified
PASP	pulmonary arterial systolic pressure
PHI	protected health information
PLR	Physician Labeling Rule
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PR	PR interval
PP	Per-protocol population
PS	primary suspect

pulm	pulmonary
PVC	premature ventricular complex
QA	quality analysis
QRS	QRS interval
QT	QT interval
QTc	QT interval, corrected
REMS	Risk Evaluation and Mitigation Strategies
RR	RR interval
RTCE	real-time contrast echocardiography
SAE	serious adverse event
SAF	Safety-evaluable population
SDI	SDI Health, LLC
SS	secondary suspect
TEAE	treatment emergent adverse event
U.S.	United States
VA	U.S. Department of Veterans Affairs
VF	ventricular fibrillation
VHS	video home system
VT	ventricular tachycardia
WBC	white blood cells

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends a complete response (CR) regulatory action for this labeling supplement because of failed negotiations with the Sponsor to produce an acceptable revised package insert for Definity.

(b) (4)

With regard to safety, the reviewer has determined that the sponsor has provided important new data from a registry study and a pulmonary hemodynamic study. The reviewer does not find the submitted retrospective observational study data to be persuasive. The reviewer does not agree with the sponsor's proposal to drastically alter the warnings in the package insert including removal of the boxed warning. However, the reviewer recommends modification of the boxed warning and updating other safety information to reflect current understanding.

1.2 Risk Benefit Assessment

The risk-benefit profile of Definity remains favorable. Definity provides important additional structural delineation, and thus important information about the heart, in the appropriate clinical setting. This information can be crucial in clinical care. Serious cardiopulmonary and anaphylactoid events are observed in association with Definity administration, but are uncommon. Causality is not always clear as the patients who receive Definity commonly have serious underlying cardiac comorbidities, may be receiving multiple concomitant medications, and may receive Definity in the off-label setting of stress echocardiography.

Overall, the submitted safety and postmarketing data suggest that the serious adverse reaction rate for Definity is reasonably low. While there are limitations with many of the data sources, and while there is significant uncertainty when estimating event rates from data such as spontaneous postmarketing reports, the present data are consistent with an estimated serious event rate between 1:100-1:1000.

However, serious cardiopulmonary events and fatalities are still observed, even after labeling changes made in 2007 and 2008. It is difficult to clearly establish causality, particularly in the patient population and setting in which Definity is commonly administered, but there is evidence that Definity has at least a partial contributory role. Many of these events occur within 30 minutes of administration, underscoring the

importance of proper warning, patient observation, and the availability of life-supporting equipment and trained personnel.

Given the persistence of these events, the reviewer recommends keeping the boxed warning in the Definity label. However, some label modifications are necessary to better reflect our current understanding of the clinical picture. The reviewer recommends better describing our understanding of the incidence of serious reactions by using the word “uncommon” in the description of the serious events. The submitted safety data supports removing the specific pulse oximetry and ECG monitoring requirements. We continue to recommend observation of all patients as many of the serious events occur within 30 minutes.



It should be noted that the sponsor has not requested a new indication, but has proposed removing the statement:

The safety and efficacy of DEFINITY® with exercise stress or pharmacologic stress testing have not been established.

from the Indications and Usage section. This statement was added in 2007 because of lack of data on the safety of Definity in clinical use. The results of the registry study and the pulmonary hemodynamic study support removing this statement from the label.

We also recommend updating the Warnings and Precautions section and the Adverse Reactions section to reflect our current understanding. The two most robust postmarketing studies, the safety registry and pulmonary hemodynamic studies, should be included in the Clinical Trials section. The entire label should be converted to Physician Labeling Rule format.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Continued postmarketing reporting and pharmacovigilance of cardiopulmonary reactions. However, no Risk Evaluation and Mitigation Strategies (REMS) are necessary.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

DEFINITY (perflutren lipid microsphere) injectable suspension is an intravenous ultrasound contrast agent originally approved for marketing in the United States in 2001. Definity has the following Indications and Usage statement:

Activated DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

The safety and efficacy of DEFINITY® with exercise stress or pharmacologic stress testing have not been established.

Definity is supplied in a vial containing perflutren and a blend of several different lipids. Prior to usage, the mixture is activated using a proprietary activation device, which results in perflutren lipid microsphere formation. The mean diameter of the microspheres ranges from 1.1µm-3.3µm with a maximum diameter of 20µm and with 98% of the microspheres having a diameter of less than 10µm (Table 1).

Table 1: Physical Characteristics of Definity

Mean Diameter (µm)	1.1-3.3
Maximum Diameter (µm)	20
% less than 10µm	98%

By encapsulating a gas in numerous tiny lipid or protein shells, Definity provides contrast to the adjacent blood when injected intravenously and viewed by ultrasound. Definity uses perflutren gas, also called octafluoropropane, for this purpose.

Optison (perflutren protein-type A microspheres) is the only other ultrasound contrast agent currently approved in the United States. The basic structure of Optison is similar to Definity in that it is comprised of many small lipid microspheres which contain echogenic gas. The lipid shell in Optison is composed of human serum albumin and contains the same gas as is used in Definity, namely perflutren. The microspheres in Optison are somewhat larger than in Definity (Table 2).

Table 2: Physical Characteristics of Optison

Mean Diameter (µm)	3.3-4.5
Maximum Diameter (µm)	32
% less than 10µm	95%

Echocardiograms are used to image the heart and diagnose cardiovascular diseases in a wide range of age groups, populations, and conditions. In some patients, echocardiograms without contrast do not delineate all structures of the heart and are considered suboptimal. In this setting, addition of a contrast agent such as Definity has been shown to improve the structural delineation of certain parts of the left ventricular chamber. No ultrasound contrast agent, including Definity, has an indication to evaluate physiology or detect disease.

Because there are a small number of microspheres that are greater than 10µm in diameter (slightly larger than a red blood cell), it is thought that these largest microspheres embolize in the pulmonary vasculature after injection. The majority of the microspheres, which are smaller than a red blood cell, pass through the pulmonary vasculature and can be imaged in the left ventricle or elsewhere in the systemic circulation.

2.2 Currently Available Treatments for Proposed Indications

Two ultrasound contrast agents are currently approved in the United States (Table 3).

Table 3: Currently Approved Ultrasound Contrast Agents

	NDA	Approval Date
Definity (perflutren lipid microspheres)	21064	7/31/2001
Optison (perflutren protein-type A microspheres)	20899	12/31/1997

Optison has the same indication statement as Definity:

OPTISON is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders.

The safety and efficacy of OPTISON with exercise stress or pharmacologic stress testing have not been established.

2.3 Availability of Proposed Active Ingredient in the United States

No known availability issues of the active ingredient.

2.4 Important Safety Issues and Regulatory History

Initial Approval

Because both of the existing approved ultrasound agents contain numerous small microspheres, there have been concerns related to microvascular obstruction since initial approval.

Contraindications have always included intra-arterial administration and administration in patients with known right-to-left cardiac shunts because of these concerns. Nonclinical studies showed that intravenous administration did not result in significant systemic microvascular obstruction, presumably because of filtering of the largest microspheres by the pulmonary vasculature.

The initial Warnings section also recommended caution in patients with chronic pulmonary vascular disorders because of these concerns, though initial nonclinical and clinical data did not show evidence of pulmonary compromise. The Precautions section also included a statement that the safety of microspheres in mechanical ventilation had not been studied.

It was also known at the time of initial approval that certain ultrasound techniques, specifically imaging with high mechanical index values, could cause microsphere cavitation and potentially lead to ventricular arrhythmias. This concern was reflected in the Precautions section of the original label.

A number of serious adverse events and deaths had been reported in clinical trials using Definity, but at the time it was felt that these were likely attributable to underlying cardiopulmonary conditions.

2006-2007

In 2006 and 2007, FDA became aware of a number of additional deaths temporally related to the administration of ultrasound contrast agents. These deaths generally followed cardiovascular collapse or a hypersensitivity reaction and occurred

predominantly in patients with underlying cardiac or pulmonary disease. Additionally, nonclinical studies reported significant pulmonary and systemic hemodynamic changes after administration of ultrasound contrast agents, particularly in the pig.

Because of these findings, a number of modifications were made to both the Definity and Optison labels in 2007 including addition of boxed warnings and new contraindications (Figures 1-2). FDA also required the sponsors to perform postmarketing clinical studies to further characterize the risks involved.

Figure 1: Definity Boxed Warning from 2007

WARNING: Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions, including fatalities, have occurred during or within 30 minutes following DEFINITY® administration.

- Assess all patients for the presence of any condition that precludes DEFINITY® administration (see [CONTRAINDICATIONS](#)).
- Monitor patients during and for 30 minutes following DEFINITY® administration, including vital sign measurements and electrocardiography in all patients and cutaneous oxygen saturation in patients at risk for hypoxemia. Always have resuscitation equipment and trained personnel readily available (see [WARNINGS](#)).

Figure 2: Definity Contraindications in 2007

Do not administer DEFINITY® to patients with known or suspected:

- Right-to-left, bi-directional, or transient right-to-left cardiac shunts,
- Worsening or clinically unstable congestive heart failure,
- Acute myocardial infarction or acute coronary syndromes,
- Serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval,
- Respiratory failure, as manifest by signs or symptoms of carbon dioxide retention or hypoxemia,
- Severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension due to compromised pulmonary arterial vasculature,
- Hypersensitivity to perflutren (see [WARNINGS](#)).

Do not administer DEFINITY® by intra-arterial injection.

The Warnings section was also revised to include the following subheadings with associated descriptions:

- Serious Cardiopulmonary Reactions,
- Anaphylactoid Reactions
- Systemic Embolization of Definity® in Patients with Cardiac Shunts
- High Ultrasound Mechanical Index

- QTc Prolongation

2008

Shortly after these major label revisions, the echocardiography community expressed concern that the restrictive nature of the new labeling would preclude the use of ultrasound contrast agents, especially in critically ill patients who they argued needed these agents most, and would therefore result in patient harm. Additionally, two new published reports were reviewed which suggested that the concerning nonclinical pulmonary hemodynamic changes may not translate to humans (Erb et al., 2001; Soman et al., 2000).

With this updated information, the boxed warning was revised to focus more specifically on those populations felt to be most at risk (Figure 3).

Figure 3: Modifications to the Black Box Warning in 2008

WARNING: Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration.

- Assess all patients for the presence of any condition that precludes DEFINITY® administration (see [CONTRAINDICATIONS](#)).
- In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor vital sign measurements, electrocardiography and cutaneous oxygen saturation patients during and for at least 30 minutes after DEFINITY® administration (see [WARNINGS](#)).
- Always have resuscitation equipment and trained personnel readily available.

In addition, the Contraindications section was substantively reverted to its original form, namely cardiac shunts, hypersensitivity to perflutren, and intra-arterial injection.

Advisory Committee

In addition to these labeling changes, the FDA instituted two postmarketing requirement (PMR) studies to further characterize the safety of Definity:

- A study that will utilize an existing database to compare in hospital mortality in critically ill patients undergoing echocardiography with and without the sponsor's ultrasound contrast agent.
- A clinical trial that, at a minimum, provides pulmonary hemodynamic data from at least 30 patients with known or suspected cardiac disease who are undergoing an echocardiogram with the sponsor's ultrasound contrast agent.

A third voluntary postmarketing commitment was also performed:

- A study of at least 1000 patients undergoing echocardiography with the sponsor's ultrasound contrast agent in routine clinical practice.

On June 24, 2008, the Cardiovascular and Renal Drugs Advisory Committee met to discuss the safety issues and new information related to ultrasound contrast agents. The Committee generally agreed with the assessments made by the FDA and endorsed the proposed risk assessment plans.

2008 - Present

Over the next few years, these postmarketing studies were completed and submitted to the FDA. An Advisory Committee was again convened on May 2, 2011 to discuss the results of these studies as well as interval postmarketing reports for the two ultrasound contrast agents approved in the United States (Definity and Optison) as well as an investigational agent that is approved and widely used in Europe and Asia (SonoVue). Lantheus Medical Imaging also submitted the supplementary NDA under review which included the results of these postmarketing studies with additional material to support both efficacy and safety changes.

2.5 Other Relevant Background Information

The ultrasound contrast agents have generally been considered as a class with similar mechanism of action and similar adverse event profiles. Similar findings and adverse events as those discussed above have been observed with Optison, currently the only other FDA approved ultrasound contrast agent. Because of this, virtually identical safety labeling changes were made for Optison along with Definity.

Several other investigational ultrasound contrast agents also exist, the most prominent in the U.S. being SonoVue, which is currently marketed in many foreign countries. A similar adverse event profile has been seen with SonoVue in both clinical trial and foreign postmarketing experience.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Data quality and integrity are acceptable. Site inspections were not performed by the Agency as this is a supplemental application.

3.2 Compliance with Good Clinical Practices

A statement of Good Clinical Practice was submitted for DMP 115-415, DMP 115-416, and DMP 115-501 including all of the individual trials that comprised DMP 115-501.

The final study report for DMP 115-419 states that the study was conducted in conformance with all applicable country and local requirements regarding ethical committee review and informed consent. The remaining data are retrospective reviews, literature reviews, or postmarketing safety reports.

3.3 Financial Disclosures

A Financial Certification and Disclosure form was submitted. Several investigators in DMP 115-415 have received speakers honoraria totaling greater than \$25,000, but there does not appear to be substantial conflict of interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No additional data are needed, nor were any new data submitted.

4.2 Clinical Microbiology

No additional data are needed, nor were any new data submitted.

4.3 Preclinical Pharmacology/Toxicology

No additional data are needed, nor were any new data submitted.

4.4 Clinical Pharmacology

No additional data are needed, nor were any new data submitted.

4.4.1 Mechanism of Action

No additional data are needed, nor were any new data submitted.

4.4.2 Pharmacodynamics

No additional data are needed, nor were any new data submitted.

4.4.3 Pharmacokinetics

No additional data are needed, nor were any new data submitted.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Nine reports were submitted for review. Four of these are studies in the setting of rest echocardiography and are focused on safety. (b) (4)

(b) (4)
 (Table 4).

Table 4: Studies submitted in the sNDA

	Title	Description
Rest	* DMP 115-415	Open-label, nonrandomized, post-marketing registry focused on safety. 1053 patients were enrolled who received echocardiograms with Definity in typical clinical practice.
	* DMP 115-416	Open-label, nonrandomized, multicenter study of pulmonary hemodynamics in 32 patients with and without pulmonary hypertension.
	* DMP 115-418	Retrospective, observational database review of mortality in critically ill patients who received echocardiograms. Patients who received echocardiograms with Definity were matched to patients who received noncontrast echocardiograms using propensity score matching techniques.

(b) (4)

(b) (4)

* These studies were post-marketing commitments or requirements that were established as part of a risk assessment plan along with the labeling changes in 2007-2008.

5.2 Review Strategy

The reviewer focused on the assessment of safety and efficacy primarily in the indicated population and secondarily in the broader clinical use population. The studies in the setting of rest echocardiography focused on safety and these were evaluated both

individually and cumulatively. The postmarketing requirements and commitments described above focused on safety and were also reviewed in an Advisory Committee meeting along with a review of spontaneous postmarketing data. The discussions and advice given by the AC is summarized in the review. (b) (4)

For both the safety and efficacy reviews both summary data and individual patient listings were examined. The reviewer performed analyses of the raw safety and efficacy data for the purpose of verification (e.g. summary statistics, patient disposition, missing data etc) and for exploratory analyses (e.g. individual variability and outlier analyses).

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Efficacy

(b) (4)

(b) (4)

The individual protocols and study reports for each of the 5 included trials were also reviewed. Raw data from the submission was analyzed to confirm the sponsor's analyses as well as to perform original analyses to help clarify areas of ambiguity and to perform exploratory analyses.

5.3.2 Safety

Four safety studies were performed in the setting of rest echocardiography. Two of these were post-marketing requirements established as part of a risk assessment plan established in 2007 because of concerning spontaneous postmarketing reports and other findings. A third was a post-marketing commitment established shortly after initial approval that was included as part of the risk assessment plan.

DMP 115-418 was a post-marketing requirement established because of a lack of safety data in the critically ill population. This trial was a retrospective, observational database review of a large number of patients using propensity score matching techniques.

DMP 115-416 was a post-marketing requirement because of concerning pulmonary hemodynamic findings in pigs. This study focused on pulmonary hemodynamic changes after Definity administration in a small group of subjects with pulmonary hypertension. Adverse events, vital signs, ECGs, and laboratory measurements were also evaluated.

DMP 115-415 was a post-marketing commitment which was a prospective safety registry of 1053 patients who underwent echocardiograms with Definity in routine clinical practice. Adverse events, vital signs, and ECG data was recorded.

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6 Review of Efficacy

Efficacy Summary

[Redacted] (b) (4)

6.1 Indication

The original indication for Definity from 2001 is as follows:

Activated DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

In 2007, an additional statement was added immediately after the indication which reflected concerns about lack of safety data in the setting of stress echocardiography with Definity and which read:

The safety and efficacy of DEFINITY® with exercise stress or pharmacologic stress testing have not been established.

The sponsor has not proposed to add a new indication in the setting of stress, rather they have proposed removing the additional statement described above that was added in 2007.

In addition, they propose including [REDACTED] (b) (4)
[REDACTED] data from their postmarketing commitment
and requirements, [REDACTED] (b) (4)

6.1.1 Methods

[REDACTED] (b) (4)

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7 Review of Safety

Safety Summary

Safety data has been submitted from a wide variety of sources

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Three studies, in the setting of rest echocardiography, were postmarketing commitments and requirements that were performed in conjunction with an FDA safety plan after the labeling changes in 2007-2008. The results of these three studies were presented at an FDA Advisory Committee meeting on May 2, 2011. While these studies have important limitations, particularly the retrospective database review, there is reasonable assurance that the serious adverse reaction rate with Definity is low, even in a patient population that is less stable and affected by more complicating factors than the narrow population evaluated in the premarket studies.

(b) (4)

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(b) (4)

7.1 Methods

Seven reports of safety data are submitted, four for Definity echocardiography at rest

(b) (4)

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 16: Studies Used to Evaluate Safety

	Study Title	Description
Rest	* DMP 115-415	Open-label, nonrandomized, post-marketing registry focused on safety. 1053 patients were enrolled who received echocardiograms with Definity in typical clinical practice.
	* DMP 115-416	Open-label, nonrandomized, multicenter study of pulmonary hemodynamics in 32 patients with and without pulmonary hypertension.
	* DMP 115-418	Retrospective, observational database review of mortality in critically ill patients who received echocardiograms. Patients who received echocardiograms with Definity were matched to patients who received noncontrast echocardiograms using propensity score matching techniques.
(b) (4)		
(b) (4)		

* These trials were post-marketing commitments or requirements that were established as part of a risk assessment plan along with the labeling changes in 2007-2008.

7.1.2 Categorization of Adverse Events

The Integrated Summary of Safety provides a description of how adverse events (AE), treatment emergent adverse events (TEAE), and serious adverse events (SAE) are categorized.

All adverse events, including observed and patient volunteered events, were recorded as adverse events regardless of the assessment of causality. An adverse event was considered treatment emergent if:

- it appeared for the first time on or after the first dose of the study drug
- it represented an exacerbation of a condition observed pretreatment

Serious adverse events were defined as any event that met any of the following criteria:

- resulted in death
- was life threatening at the time of the event
- required in-patient hospitalization or prolongation of an existing hospitalization

- resulted in persistent or significant disability/incapacity defined as a substantial disruption of a person's ability to conduct normal life functions
- was a congenital anomaly/birth defect
- was an important medical event that, when based upon appropriate medical judgment, may have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

(b) (4)

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Approximately 80,000 patients were exposed to at least one dose of Definity in the seven trials focused on safety. Most patients were adults with mean ages ranging from 56-66 (b) (4). Some patients were exposed in the setting of rest echocardiography and some in stress. Dosing schemes were variable across these trials and were absent in two trials. Many of the patients received more than the label recommended dose.

Nearly 2 million patients who underwent noncontrast echocardiograms were included in these trials using various methodologies. These largely come from DMP 115-418, the retrospective database review, (b) (4). Mean ages for these patients ranged from 56-67.

DMP 115-415

All patients in this trial received single or multiple bolus dosing of Definity.

In rest, 1018 patients received a mean dose of 0.475 mL (range 0.05-2 mL) corresponding with a mean weight based dosing of 5.15 microL/kg (range 0.42-23 microL/kg) with 32 patients receiving one bolus dose higher than the labeled recommendation and one additional patient receiving multiple boluses with a total dose higher than the labeled recommendation. Three patients did not have reported dose information in rest.

In stress, 452 patients received a mean dose of 0.499 mL (range 0.09-2.1 mL) corresponding with a mean weight based dosing of 5.32 microL/kg (range 0.67-30.9 microL/kg) with 15 patients receiving one bolus dose higher than the labeled

recommendation and two additional patients receiving multiple boluses with a total dose higher than the labeled recommendation. Two patients did not have reported dose information in stress.

Slightly more patients in this trial were under 65 years of age. More patients were male than female. The majority of patients were white (Table 17).

Table 17: DMP 115-415 - Demographics

Age (years)	Mean ± SD	61.3 ± 12.9
	<65	57.8%
	≥65	42.2%
Gender	Male	62.0%
	Female	38.0%
Race	White	81.5%
	Asian	1.2%
	African American	14.3%
	Other	2.4%

DMP 115-416

A total of 32 patients received a mean Definity dose of 1.0 mL (range 0.5-1.5mL) with a weight-based mean dose of 11.73 microL/kg (range 9.09-25.59 microL/kg). 16 patients received more than the label recommended dose.

The 16 patients who had pulmonary hypertension at baseline received a mean Definity dose of 0.91 mL (range 0.5-1.3 mL) with a weight-based mean dose of 11.38 microL/kg (range 9.09-20 microL/kg). Seven of these patients received more than the label recommended dose.

The 16 patients who had normal pulmonary pressures at baseline received a mean Definity dose of 1.09 mL (range 0.7-1.5 mL) with a weight-based mean dose of 12.1 microL/kg (range 9.52-25.59 microL/kg). Nine of these patients received more than the label recommended dose.

More patients in this trial were under 65 years of age. More patients were male in the normal pulmonary pressure group, but more patients were female in the pulmonary hypertension group. The majority of patients were white (Table 18).

Table 18: DMP 115-416 - Demographics

		Pulmonary Hypertension (n=16)	Normal (n=16)
Age (years)	Mean ± SD	57.4±15.1	56.9±10.8
	<65	68.8%	68.8%
	≥65	31.3%	31.3%
Gender	Male	56.3%	37.5%
	Female	43.8%	62.5%
Race	White	62.5%	68.8%
	African American	25.0%	0%
	Other	12.5%	31.3%

DMP 115-418

A total of 16,223 patients who received Definity in association with an echocardiogram were included in this retrospective database review. Patients who underwent stress echocardiography only were excluded, however some patients included in the evaluation may have undergone rest and stress echocardiography. Specific dose information was not available in the database.

More patients in this trial were 65 years of age or older. More patients were male. Most patients were white. There are some differences in demographics between the noncontrast and Definity groups, but the analyses in this trial used propensity score techniques to match patients to account for these differences (Table 19).

Table 19: DMP 115-418 - Demographics

		Noncontrast (n=991,983)	Definity (n=16,223)
Age (years)	Mean ± SD	66.8±15.5	65.0±13.9
	<65	40.2%	46.6%
	≥65	59.8%	53.4%
Gender	Male	51.8%	63.5%
	Female	48.2%	36.5%
Race	White	64.8%	73.9%
	African American	14.3%	11.2%
	Hispanic	4.9%	1.6%
	Other	16.1%	13.4%

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7.2.2 Explorations for Dose Response

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Data from DMP 115-415, the observational study of 1053 patients who received Definity in routine medical practice, was broken down by dose strata. No relationship between dose and adverse event reporting rate was identified.

7.2.3 Special Animal and/or In Vitro Testing

No animal or in-vitro testing was performed as part of this supplementary application.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No pharmacologic assessments were made as part of this supplementary application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Data on the safety of Optison were provided by its manufacturer in a briefing package and were presented at the May 2, 2011 FDA Advisory Committee meeting. A similar

adverse event profile is observed for Optison. Serious adverse events observed in clinical trials and spontaneous postmarketing reporting are typically cardiopulmonary or anaphylactoid in nature, and commonly occur within minutes of administration. Similar to Definity, there are many confounding factors and concomitant interventions in the population in which Optison is used which makes elucidation of causality very difficult.

7.3 Major Safety Results

7.3.1 Deaths

DMP 115-415

No deaths were observed in this trial.

DMP 115-416

No deaths were observed in this trial.

DMP 115-418

In this retrospective database review, 353 total fatalities are reported in patients who received Definity in the same hospitalization, though establishing causality is not possible given the limitations of the billing database used. A total of 25,626 fatalities are reported in patients who underwent noncontrast echocardiograms in the same hospitalization (Table 26).

Table 26: DMP 115-418 - Mortality in All Patients

	Definity	Noncontrast
Patients	16,223	991,983
Deaths	353	25,626
Death Rate	2.18%	2.58%

Mortality in matched contrast and noncontrast datasets after propensity score matching techniques were applied is provided for both sponsor and FDA analysis (Table 27).

Table 27: DMP 115-418 - Mortality in Matched Datasets

		Sponsor Analysis		FDA Analysis	
		Definity	Noncontrast	Definity	Noncontrast
	Patients	15,798	15,798	16,199	16,199
Same Day or Next Day Mortality	Deaths	338	488	353	443
	Death Rate	2.14%	3.09%	2.18%	2.73%
All In-Hospital Mortality	Deaths	2321	2616	2401	2619
	Death Rate	14.69%	16.56%	14.85%	16.17%

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7.3.2 Nonfatal Serious Adverse Events

DMP 115-415

No serious adverse events were observed in this trial.

DMP 115-416

No serious adverse events were observed in this trial.

DMP 115-418

Serious adverse events were not reported in the database used in this retrospective analysis.

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7.3.3 Dropouts and/or Discontinuations

DMP 115-415

A total of seven patients were discontinued prior to receiving Definity, five because of inability to obtain IV access, one because of a ventricular septal defect, and one because of patient withdrawing consent. No discontinuations were due to adverse events or protocol violations.

DMP 115-416

Two patients were discontinued prior to receiving Definity. One patient required an urgent intervention and one patient met exclusion criteria of baseline pulmonary arterial systolic pressure greater than 75 mmHg. No dropouts or discontinuations occurred after receiving Definity.

DMP 115-418

Not applicable in this retrospective database review.

7.3.4 Significant Adverse Events

DMP 115-415

No significant adverse events were observed in this trial.

DMP 115-416

One patient experienced two adverse events, lower back pain and headache, that were moderate in intensity and were considered possibly related to Definity. These adverse events were also considered possibly related to pulmonary arterial catheterization. These adverse events resolved with medication.

DMP 115-418

Adverse events were not reported in the database used in this retrospective analysis.

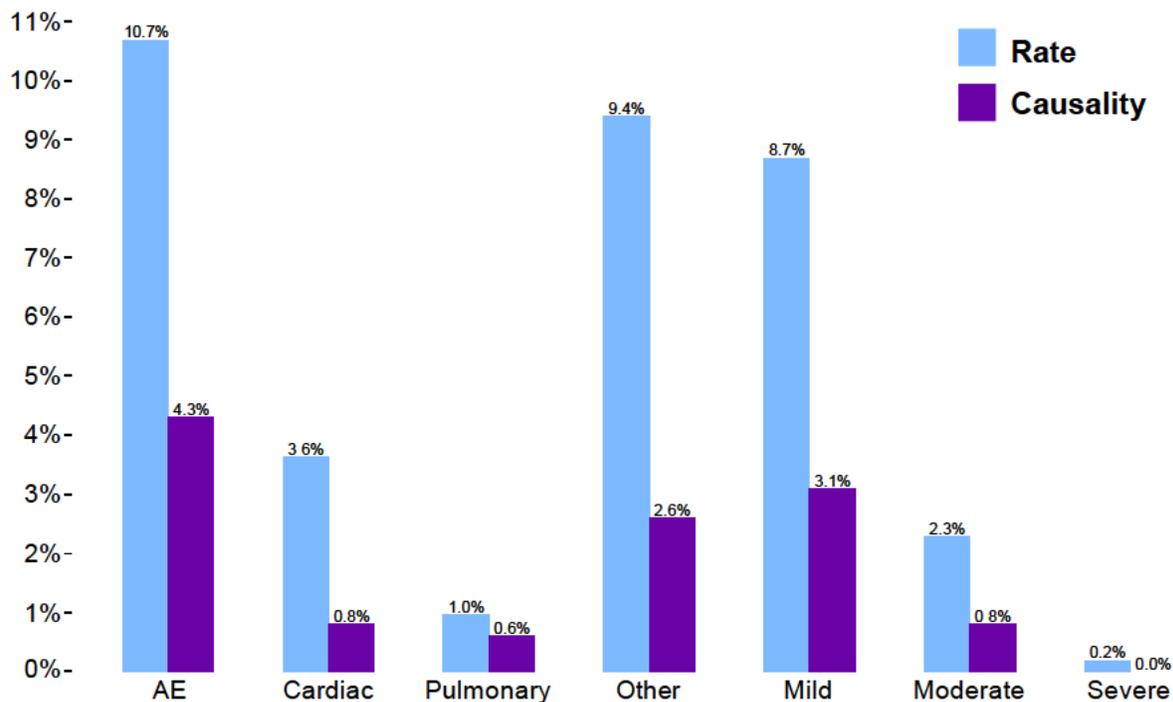
7.4 Supportive Safety Results

7.4.1 Common Adverse Events

DMP 115-415

Based on reviewer analysis of raw data, adverse events were observed in 10.7% of patients with 4.3% of patients experiencing adverse events that were considered possibly related to Definity. These numbers are similar to those reported by the sponsor with slight differences likely related to the reviewer's exclusion of five patients without dosing information. 85% of the observed adverse events occurred within 30 minutes of administration. The vast majority were mild or moderate in intensity with very few being severe in intensity. No relationship between dose and adverse event rate was observed (Figure 20).

Figure 20: DMP 115-415 - Adverse Events



The most common adverse events with a reporting rate greater than 0.5% are below (Table 34).

Table 34: DMP 115-415 - Most Common Adverse Events

Adverse Event	Rate
Headache	1.2%
Nausea	0.9%
Back Pain	0.7%
Tremor	0.6%
Angina Pectoris	0.5%
Chest Pain	0.5%
Palpitations	0.5%
Ventricular Extrasystoles	0.5%
Dizziness	0.5%
Flushing	0.5%

DMP 115-416

Nine patients experienced adverse events in this trial, four in the normal pulmonary pressure group and five in the pulmonary hypertension group. One patient in the normal pulmonary pressure group experienced two adverse events (lower back pain and headache) that were moderate in intensity and which resolved with medication. The remainder of the adverse events were mild in intensity.

The most common adverse events occurring in more than 0.5% of patients are listed below. Because of the relatively small number of patients in this trial, all adverse events reported have an incidence of greater than 0.5% (Table 35).

Table 35: DMP 115-416 - Most Common Adverse Events

Adverse Event	Rate
Myalgia	15.6%
Lower Back Pain	6.3%
Chest Pain	3.1%
Neck Pain	3.1%
Dizziness	3.1%
Headache	3.1%

DMP 115-418

Adverse events were not reported in the database used in this retrospective analysis.

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7.4.2 Laboratory Findings

DMP 115-415

Laboratory measures were not evaluated in this trial.

DMP 115-416

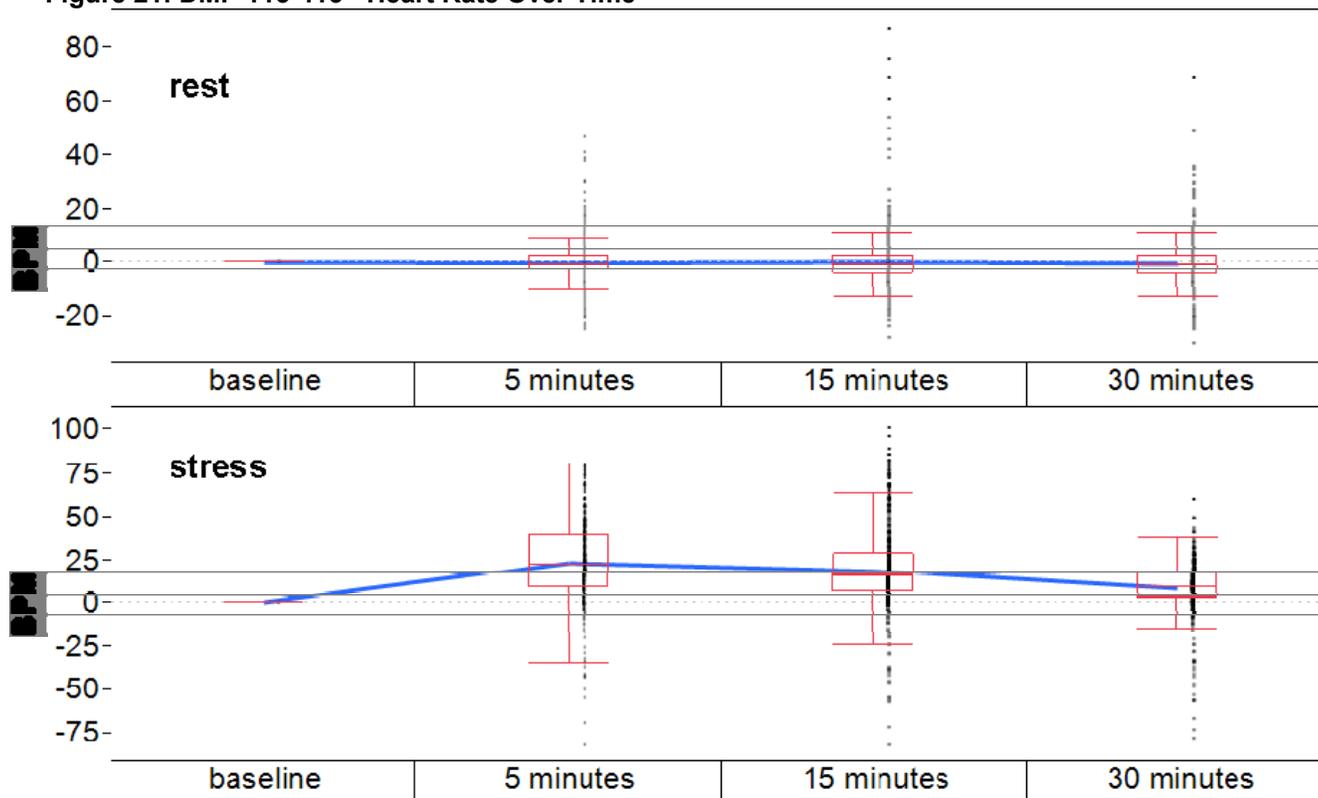
No clinically important chemistry or hematology laboratory changes were observed in this trial. Interesting, but inconclusive, changes in some immunologic parameters were seen and are described below (Section 7.4.6).

7.4.3 Vital Signs

DMP 115-415

No clinically important vital sign changes were seen in this trial. A representative chart of vital sign changes over time is provided below. In this chart, change in mean heart rate is shown at various timepoints after Definity administration. The blue line connects the mean change. The red boxes represent the 25-75th percentiles. The whiskers represent the 10-90th percentiles. The dots represent individual patients or clusters of patients and are provided to give a sense of individual variability. The chart is divided into those patients that underwent rest echocardiography and those patients who underwent stress echocardiography. As expected, heart rate increases during stress followed by recovery over time. In both cases, there is some expected individual variability, but no concerning patterns. Similar findings were seen for other vital sign measurements (Figure 21).

Figure 21: DMP 115-415 - Heart Rate Over Time

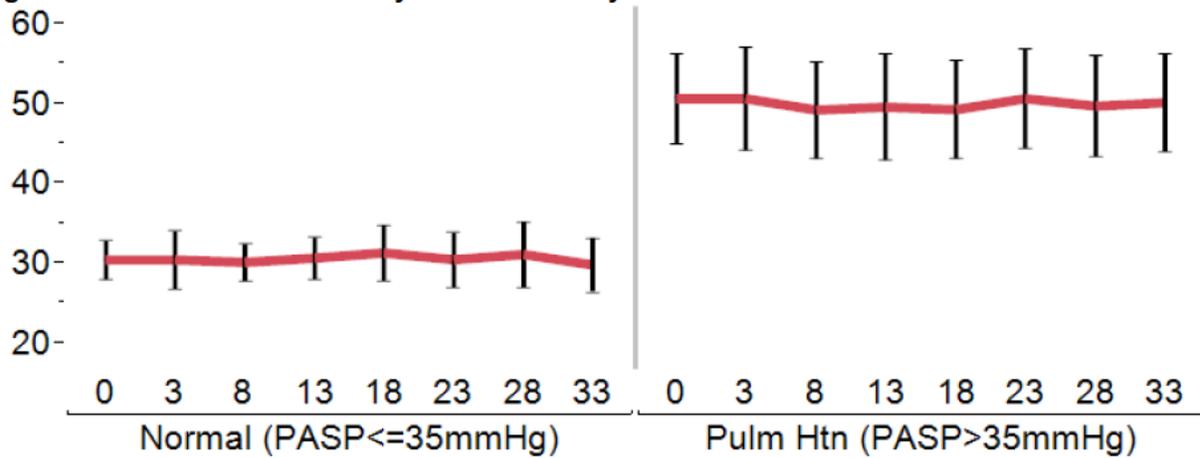


DMP 115-416

No clinically important changes were seen in pulmonary nor systemic hemodynamic parameters in either patients with normal baseline pulmonary pressures or patients with pulmonary hypertension. Some individual variability was seen for each of the parameters, but no clear patterns were seen. A representative chart of mean systolic pulmonary arterial pressure over time is displayed. Patients with normal pulmonary pressures are on the left and patients with pulmonary hypertension are on the right.

The red lines connect the mean values over time and the black bars represent 95% confidence intervals (Figure 22).

Figure 22: DMP 115-416 - Mean Systolic Pulmonary Arterial Pressure Over Time



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7.4.4 Electrocardiograms (ECGs)

DMP 115-415

No clinically significant ECG changes were observed in this trial. A substantial number of ECG interpretations changed from normal to abnormal or demonstrated a new cardiac abnormality after the stress dose, particularly early in stress, but most of these changes were rhythm changes such as sinus tachycardia, premature ventricular contractions, or premature atrial contractions. These changes are expected during stress testing and in a patient population with underlying cardiac conditions. Small percentages of ECG interpretations changed from normal to abnormal in the rest population (Table 39).

Table 39: DMP 115-415 - ECG Changes

	Rest Dose			Stress Dose		
	5 Min.	15 Min.	30 Min.	5 Min.	15 Min.	30 Min.
Overall Interpretation	489 (52.0%)	415 (59.6%)	399 (60.4%)	188 (45.0%)	141 (33.5%)	112 (25.6%)
Normal at Baseline That Remain Normal	416 (44.3%)	258 (37.1%)	239 (36.2%)	210 (50.2%)	259 (61.5%)	289 (66.0%)
Normal at Baseline That Become Abnormal	21 (2.2%)	23 (3.3%)	16 (2.4%)	85 (20.3%)	45 (10.7%)	22 (5.0%)
Patients Developed a New Cardiac Rhythm Abnormality*	15 (1.6%)	12 (1.7%)	4 (0.6%)	66 (15.8%)	12 (2.9%)	4 (0.9%)

*Patient develops a type of ECG abnormality that was not reported on pre-dose page.

The QT interdisciplinary review team was consulted regarding these data. The reported that the data is inconclusive because no central over-read was performed and ECG data was not collected at appropriate timepoints.

DMP 115-416

ECGs were obtained at baseline and two hours after Definity administration. Baseline abnormalities were noted in a number of patients which is expected in this patient population. No clinically significant variations in interpretation were observed. No clinically significant changes in QT, QTc, QRS, PR, or RR intervals were seen.

The QT interdisciplinary review team was consulted regarding these data. The reported that the data is inconclusive because no central over-read was performed and ECG data was not collected at appropriate timepoints.

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7.4.5 Special Safety Studies/Clinical Trials

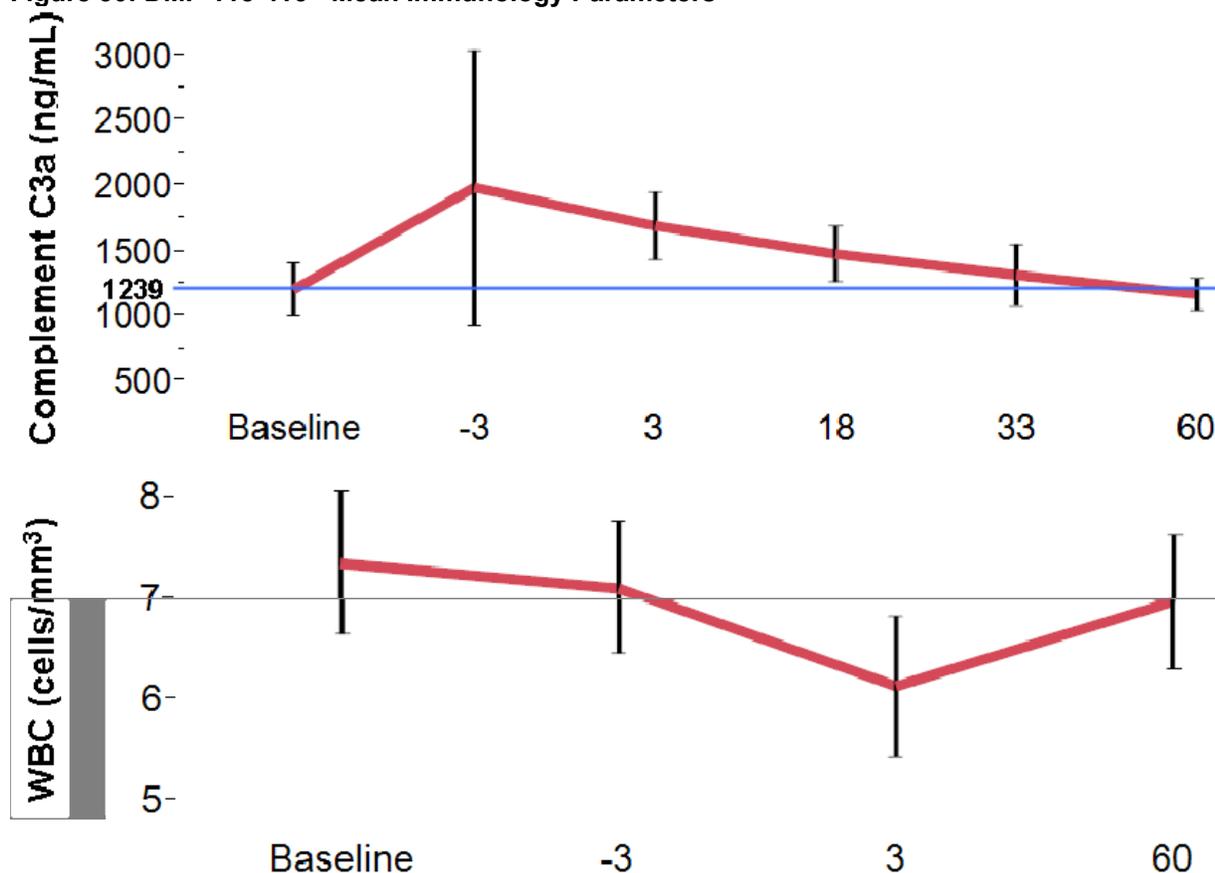
7.4.6 Immunogenicity

DMP 115-416

Several immunologic laboratory measures were obtained in this trial. The mean complement C3a level at three minutes after Definity administration was significantly higher than at baseline, and subsequently slowly trended downwards towards baseline over time. Mean white blood cell levels decreased at three minutes after Definity administration, though this change was not significant. These findings were suggestive of complement activation with white cell migration which could represent activation of the immune system.

However, at three minutes prior to administration, the complement C3a level was actually higher than at three minutes after administration, though not significantly different due to a wide 95% confidence interval. The wide confidence interval appears to be related to at least one outlier measurement at this timepoint, though even after removal of the outlier the mean value at three minutes prior to administration is not significantly different than at three minutes after administration. In this trial, 1239 ng/mL was the upper limit of normal (Figure 30).

Figure 30: DMP 115-416 - Mean Immunology Parameters



7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

DMP 115-415

When patients were stratified by Definity dose, no relationship between dose and adverse event rate was observed.

7.5.2 Time Dependency for Adverse Events

The sponsor reports on their clinical trial experience in the setting of stress. Postmarketing data is also available, of which a substantial portion of patients were probably exposed in the setting of stress. Many serious adverse events occur within 30 minutes of administration (Table 40).

Table 40: Time Dependency of Adverse Events

		Total	Within 30 minutes	Within 60 minutes	More than 60 minutes
Clinical Trials in Stress	SAE	10	5	6	4
Postmarketing Experience	Deaths	22	14	17	5
	SAE*	330	184	187	9

* 133 unclear time to onset

* One postmarketing report was a medication/labeling error

7.5.3 Drug-Demographic Interactions

DMP 115-415

Adverse event rates were similar when patients less than 65 years of age are compared to those who are 65 years of age or greater. A higher adverse event rate was observed in females compared to males. Variable adverse event rates in the various ethnic subgroups are somewhat difficult to interpret because of the relatively low number of non-Caucasian patients in this trial (Table 41).

Table 41: DMP 115-415 - Subgroup Adverse Event Rate

Subgroup	Adverse Event Rate
Total	10.7%
<65	10.4%
≥65	10.6%
Male	8.8%
Female	13.3%
Caucasian	11.1%
African American	6.7%
Asian	15.4%
Other	9.7%

7.5.4 Drug-Disease Interactions

The submitted trials were not designed nor powered to evaluate drug-disease interactions. Definity is typically administered infrequently and as a single dose which makes this less of a concern.

7.5.5 Drug-Drug Interactions

The submitted trials were not designed nor powered to evaluate drug-drug interactions. Definity is typically administered infrequently as a single dose, and has a short half-life, which makes this less of a concern.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity is not a concern given the dosing scheme of Definity.

7.6.2 Human Reproduction and Pregnancy Data

Definity is considered Pregnancy Category B. No adequate and well-controlled studies of Definity have been performed in pregnant women. Nonclinical reproductive studies revealed no evidence of impaired fertility or harm to the fetus due to Definity.

This submission did not further address human reproduction or pregnancy concerns.

7.6.3

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7.6.4 Other Subgroup Analyses

Adverse event rates appear to be similar across age groups, gender, and race when the entire clinical trial and postmarketing experience is considered. No clear pattern for any particular subgroup is identified.

7.6.5 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable given the dosing scheme for Definity.

7.7 Additional Submissions / Safety Issues

DMP 115-418

As discussed in Appendix 9.3, Advisory Committee, below, this study had critical limitations that limited its usefulness.

8 Postmarket Experience

8.1 Deaths

A total of 22 unique postmarketing deaths have been reported in association with Definity as of the end of 2010. Of these 22 deaths, 14 occurred within 30 minutes of administration and 17 occurred within 60 minutes of administration. Four of these deaths were clearly associated with stress testing, two with exercise and two with dobutamine. The majority of these deaths appeared to be cardiopulmonary and/or anaphylactoid in nature and were typically followed by cardiac arrest or coding. Example descriptions of several of these deaths are provided (Table 42).

Table 42: Definity - Example Postmarketing Fatal Adverse Event Reports

Causality (reporter assessment)	Example Fatal Adverse Events
PS	"infusion reaction shortly after administration [with] full cardiac arrest 15 minutes after receiving perflutren."
PS	"Approximately 3 minutes after administration, he complained of a sensation of 'tingling'... the patient was centrally cyanotic, unresponsive, and apparently seizing. The physician felt this was likely a hypersensitivity reaction...despite aggressive and prolonged resuscitative efforts, the patient expired."
PS	"After 4 minutes of perflutren administration, the patient developed what appeared to be an anaphylactoid reaction with a fatal outcome."

* PS = primary suspect agent

8.2 Adverse Events

A total of 1340 adverse events are reported in the AERS database as of February 14, 2011 where Definity was reported as the primary or secondary suspect drug with a peak

number of adverse events of 393 reported in 2007. Of all adverse events, 264 were reported as serious adverse events with a peak of 68 reported in 2007.

Many of these adverse events appeared to be cardiopulmonary or anaphylactoid in nature and of those with time information, many appeared to occur shortly after administration. Example descriptions of several of these events is provided (Table 43).

Table 43: Definity - Example Postmarketing Adverse Event Reports

Causality (reporter assessment)	Example Adverse Events
PS	“...[patient] developed flushing, redness, shortness of breath, hypotension, and a drop in oxygen level less than one minute after receiving Definity...”
PS	“...experienced pain and coded after receiving a diluted bolus of 1.3mL of perflutren... He began to experience pain within 1 minute of the introduction of perflutren.”
PS	“...developed life-threatening ventricular fibrillation 2 minutes after receiving two doses of perflutren...”

* PS = primary suspect agent

8.3 Utilization

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9 Appendices

9.1 Literature Review/References

Erb JM, Shanewise JS. Intraoperative contrast echocardiography with Optison does not cause hemodynamic changes during cardiac surgery. J Am Soc Echocardiogr 2001;14:595-600.

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Rogers AS, Israel E, Smith CR, et al. Physician knowledge, attitudes, and behavior related to reporting adverse drug events. Arch Intern Med. 1988;148:1596-1600.

Scott HD, Rosenbaum SE, Waters WJ, et al. Rhode Island physicians' recognition and reporting of adverse drug reactions. Rhode Island Medical Journal. 1987;July:311-6.

Soman P, Lahiri A, Senior R. Safety of an intravenous second generation contrast agent in patients with severe left ventricular dysfunction. Heart; 2000;84:634-635.

9.2 Labeling Recommendations

Boxed Warning

Recommend keeping the boxed warning, but including the word “uncommon” as an estimate of the rate of serious adverse reactions to Definity. We also recommend removing the specific pulse oximetry and ECG monitoring requirements and replacing them with a general observation recommendation.

1 Indications and Usage

Recommend removing the statement that safety and efficacy with stress have not been established. Otherwise, the indication should remain the same.

4 Contraindications

The Contraindications section should remain the same.

5 Warnings and Precautions

Recommend changing the language to be consistent with the boxed warning and updating the list of symptoms observed.

6 Adverse Reactions

6.2 Postmarketing Experience

Recommend updating the list of terms based on new reports.

8 Use in Specific Populations

8.1 Pregnancy

Recommend updating this section to be compatible with new requirements. No new pregnancy data is submitted.

8.2 Labor and Delivery

Recommend omitting this section upon consultation with the maternal health team as no relevant data is available.

8.3 Nursing Mothers

Recommend updating this section in consultation with the maternal health team based on known pharmacodynamics of Definity.

8.4 Pediatric Use

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8.5 Geriatric Use

Recommend updating this section to provide actual numbers of patients studied in the geriatric subgroup.

9 Drug Abuse and Dependence

Recommend omitting this section as it is not relevant.

14 Clinical Studies

Recommend including the results of the postmarketing safety registry and pulmonary hemodynamic studies as these studies were relatively robust and support safety labeling changes.

Formatting

Recommend updating the label to Physician Labeling Rule format.

9.3 Advisory Committee Meeting

A joint meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees was held on May 2, 2011. The focus was on safety data related to three ultrasound contrast agents, Definity and Optison which are currently approved in the U.S., and SonoVue which is approved elsewhere but currently has investigational status in the U.S. Emphasis was placed on interval safety data since the prior Advisory Committee meeting related to the safety of these agents which was held on June 24, 2008.

The sources of data included three postmarketing studies that Lantheus Medical Imaging and GE Healthcare performed for their ultrasound contrast agents, Definity and Optison, respectively. Postmarketing reporting data since approval was also reviewed

for both agents. Bracco Diagnostics provided a summary of their clinical trial and foreign postmarketing experience for SonoVue.

In regards to the three postmarketing studies for Definity and Optison, one clear conclusion from the committee was that the retrospective database reviews had multiple critical limitations that significantly limited their usefulness. There was a brief discussion about how one might re-analyze this data or re-perform these studies, but ultimately this was felt to be of limited usefulness. The observational studies were felt to be more useful, though they were limited by their lack of control and by their relatively low numbers of patients, particularly when attempting to quantify risk for rare events. Finally, the pulmonary hemodynamic studies, while also limited in numbers, were felt to provide reasonable assurance that no clinically important hemodynamic changes are seen after Definity or Optison administration. Overall, even given the limitations of these trials, the Committee concluded the trials were useful in ruling out a high rate of serious events.

The Committee agreed that serious adverse events and fatalities continue to be observed in spontaneous postmarketing reporting. Though causality is very difficult to assess because of significant comorbidities, concomitant medications, and in some cases associated stress procedures, the common pattern and typically short time period from administration to event was concerning. There are many limitations and uncertainties in calculating event rates from this data, but the Committee seemed reasonably assured that these events were uncommon.

There was a somewhat mixed response in the discussion over whether the boxed warning was still necessary. Some felt that while there were limitations in the postmarketing trials and postmarketing reporting, the event rates appeared low enough that a boxed warning might not be necessary. Others felt that the seriousness and concerning pattern of events warranted highlighting these concerns to clinicians. Several members noted that while the sponsors and some clinicians suggested the boxed warning was hampering use of these agents, the sales data, at least for Definity, showed a rebound after the initial labeling changes in 2007 and 2008. Most members felt that the specific monitoring requirements in the boxed warning were somewhat onerous and could perhaps be modified.

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/s/

ROSS W FILICE
07/21/2011

LIBERO L MARZELLA
07/22/2011

Summary Review for Regulatory Action

Date	July 26, 2011
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	021-064/efficacy supplement under 505b2
Applicant Name	Lantheus Medical Imaging
Date of Submission	September 29, 2010
PDUFA Goal Date	July 29, 2011
Proprietary Name / Established (USAN) Name	DEFINITY/Vial for Perflutren Lipid Microsphere Injectable Suspension
Dosage Forms / Strength	No new dosage proposed; current dosage is 10 mcL/kg bolus injection with option for second dose; may also be administered as an infusion as described in current labeling
Proposed Indication(s)	“Activated DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border (b) (4)
Action/Recommended Action:	Complete Review-response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Ross Filice, MD & Louis Marzella, MD, PhD (CDTL)
Statistical Review	Janelle Charles, PhD & LaRee Tracy, PhD (TL)
Pharmacology Toxicology Review	Not applicable/no data
CMC Review/OBP Review	Not applicable/no data
Microbiology Review	Not applicable/no data
Clinical Pharmacology Review	Christy John, PhD & Y. Gene Williams, PhD (TL)
DDMAC	James Dvorsky
DSI	Not applicable/no inspections
CDTL Review	Louis Marzella, MD, PhD
OSE/DMEPA	Not applicable
OSE/DDRE	Not applicable
Pediatric and Maternal Health	Upasana Bhatnager, MD, Jeanine Best & Karen Feibus, MD (TL)
Consultative Reviewer	Suchitra Balakrishnan/CardioRenal Drugs
Project Manager	Frank Lutterodt

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls

1. Introduction:

Definity is a “microbubble” contrast agent used in echocardiography to enhance visualization among patients with suboptimal echocardiograms. Importantly, most patients have adequate echocardiographic visualization without the use of a contrast agent. This is an important consideration because both approved echocardiographic contrast agents (Definity and Optison) have been associated with uncommon but serious cardiovascular reactions. These reactions prompted the addition of a boxed warning to the labeling in 2007 along with new contraindications other safety information. Subsequently, accumulating information led to a revision of the labeling to remove some of the contraindications (2008); this labeling approval was accompanied with a commitment for the sponsor to complete at least three clinical studies:

- a) a study of pulmonary hemodynamics;
- b) a retrospective/observational study of the use of Definity among critically ill patients;
- c) complete a previously requested post-marketing “registry” study of Definity “in actual clinical use.”

The current submission includes the three requested clinical study results plus:

(b) (4)

The safety data were discussed at a May 2, 2011 meeting of the Cardiovascular and Renal Drugs Advisory committee. The most notable advice from the Committee was the citation of many limitations within the observational study conducted among critically ill patients. The advisors expressed opinions that generally indicated these study results were not useful and potentially misleading due to uncontrolled bias as well as other limitations associated with the retrospective design.

The review team supplied proposed labeling text to the sponsor late in the review cycle (b) (4) The supplied labeling text built upon the physicians labeling rule format (PLR format) the sponsor had originally supplied with

the application. The sponsor expressed an opinion that [REDACTED] (b) (4)
[REDACTED] consequently, the review has culminated [REDACTED] (b) (4)
[REDACTED] in a complete review letter.

2. Background:

The initial development of Definity occurred among patients who had few underlying comorbidities. This consideration prompted the FDA to request (and the sponsor agreed to) a post-marketing commitment to study Definity “as it is actually used in clinical practice.” (from 2001 approval letter). However, this commitment was not fulfilled by the time post-marketing reports had begun to show serious (and sometimes fatal) reactions shortly following Definity administration (reports that culminated in the 2007 label revision). The reports of the serious reactions generally involved patients with fairly severe underlying comorbidities (ie., the types of conditions that would have generally excluded patients from premarketing studies). The FDA was also concerned in 2007 by the reports of pulmonary hypertension in animal models [REDACTED] (b) (4)
[REDACTED]

Ultimately, the FDA worked with the sponsor to develop a plan to obtain clinical data that helped to better characterize the safety of Definity. This supplement contains this safety data [REDACTED] (b) (4)
[REDACTED]

3. Chemistry, Manufacturing and Controls:

No new information.

4. Nonclinical Pharmacology/Toxicology:

No nonclinical data were submitted.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by Drs. Christy John and Gene Williams regarding the necessary text for the PLR format.

No new clinical pharmacology data were provided.

6. Clinical Microbiology:

No new data.

7. Clinical/Statistical-Efficacy:

Dr. Ross Filice provided the main clinical review and Dr. Louis Marzella provided the Cross Discipline Review.

Dr. Janelle Charles provided the main statistical review and Dr. Laree Tracy provided the supervisory review.

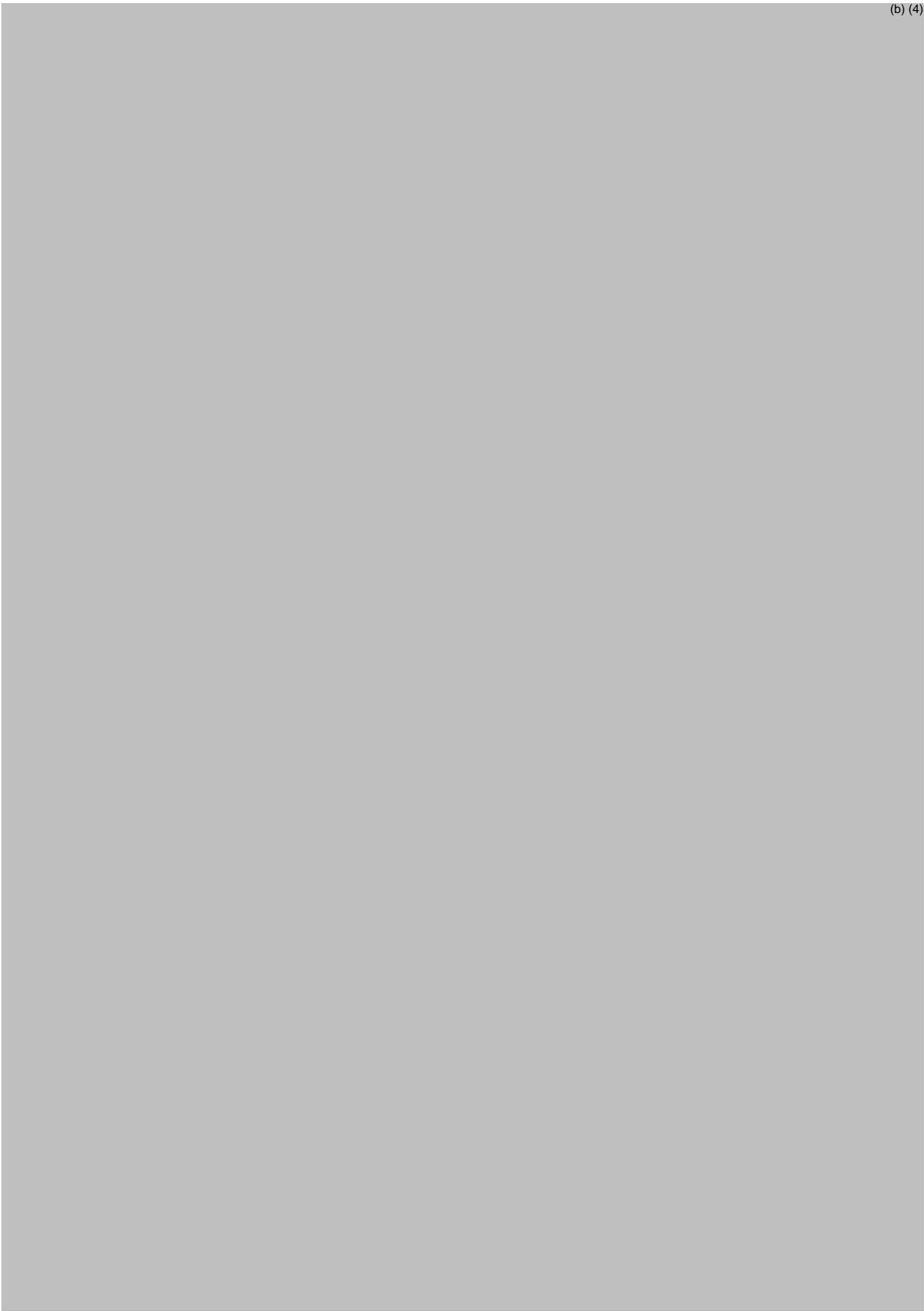
The application included the following main data sources:

Study	Features
DMP 115-415	Phase IV registry study of Definity in clinical practice
DMP 115-416	Pulmonary hemodynamics
DMP 115-418	Retrospective, observational database study of critically ill patients

(b) (4)

The data contained multiple deficiencies as summarized here and excerpted from the complete review letter.

(b) (4)





4. 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 the proposed changes to the label. However, we do not agree with elimination of the boxed warning. We supplied the sponsor with a draft version of potentially acceptable labeling during the review cycle.
 - b.  (b) (4)
Once the sponsor has addressed these concerns, we encourage the submission of revised labeling that either incorporates the edits we 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.



8. Safety:

As noted above, the supplied safety data provide useful information regarding the potential for adverse reactions to Definity. The data importantly detected no signal for pulmonary hemodynamic alterations (among relatively “stable” patients). Together, the review team concluded that modification of the prescribing information was appropriate to include some of the supplied safety data. The team did not concur with the sponsor’s proposal to remove the boxed warning.

Post-marketing Requirements (PMR): none

Post-marketing Commitments: none

9. Advisory Committee Meeting:

Safety was discussed at a May 2, 2011 advisory committee, as noted above.

10. Pediatrics:

11. Other Relevant Regulatory Issues:

No inspections were performed. Consultation was provided by the CardioRenal Drug Products review division.

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/s/

RAFEL D RIEVES
07/28/2011

Cross-Discipline Team Leader Review

Date	July 25, 2011
From	Louis Marzella MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA021064
Supplement#	11 (Efficacy)
Applicant	Lantheus Medical Imaging
Date of Submission	9/29/2010
PDUFA Goal Date	7/29/2011
Proprietary Name	Definity
Established (USAN) Name	Perflutren Lipid Microspheres
Pharmacologic Class	Ultrasound Contrast Agent
Dosage of activated drug	IV Bolus Injection: 10 microL/kg with a 10 mL saline flush; a second dose may be given 30 min later. IV Infusion: 1.3 ml in 50 ml saline at 4 to 10 ml/min
Dosage Form	Injectable suspension
Strength	(b) (4) particles/ml after activation
Administration Route	Intravenous (IV)
Proposed Indication	For use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border (b) (4)
Recommended:	Complete Response

1. Introduction

Definity: labeled indications

Definity (Perflutren Lipid Microsphere) Injectable Suspension is a diagnostic ultrasound contrast agent approved on July 31, 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. The Definity indication statement cautions that the safety and efficacy of Definity with exercise stress or pharmacologic stress testing have not been established.

Definity: drug product

The perflutren lipid microspheres are composed of octafluoropropane gas encapsulated in an outer lipid shell. After activating the contents of the vial in a proprietary mixer each mL of the milky white suspension contains a maximum of 1.2×10^{10} perflutren lipid microspheres, and about 150 microL/mL (1.1mg/mL) octafluoropropane. The mean diameter of the microspheres ranges from 1.1µm-3.3µm with a maximum diameter of 20 µm and with 98% of the microspheres having a diameter of less than 10 µm. The perflutren lipid microspheres exhibit lower acoustic impedance than blood and enhance the intrinsic backscatter of blood.

Supplemental NDA: objectives

On September 29, 2010 Lantheus Medical Imaging (the Applicant) submitted a supplemental New Drug Application with data on the use of Definity in:

- [REDACTED] (b) (4)
- current clinical practice (postmarketing commitment, PMC)
- critically ill patients (postmarketing requirement, PMR)
- patients with normal and elevated pulmonary artery pressure (postmarketing requirement)
- [REDACTED] (b) (4)

Supplemental NDA: proposed labeling

This submission also included a reformatted Definity Package Insert (PI) in Physician Labeling Rule format. The Applicant proposed extensive revisions to the following sections of the PI.

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]

Supplemental NDA: data sources

The principal objectives of the present supplemental application can be summarized as follows: [REDACTED] (b) (4), important label updates on the safety of Definity in the critically ill and in the clinical use population, [REDACTED] (b) (4). The data streams for these objectives with emphasis on their methodological weaknesses are outlined below.

[REDACTED] (b) (4)

- [Redacted] (b) (4)
- [Redacted]

- [Redacted] (b) (4)
- [Redacted]
- [Redacted]

[Redacted] (b) (4)

Definity safety studies

The submission also contains important data requested by FDA under the FDA Amendment Acts (as PMR) or negotiated with the Applicant (an outstanding PMC) for assessing the safety of Definity in critically ill patients and in the current clinical use population. The submission contains the following complete study reports.

- DMP 115-415 (Registry Study) is a prospective open-label surveillance registry study of Definity in 1053 patients in clinical practice. Adverse events, vital signs, and ECG data were captured.
- DMP 115-416 (Pulmonary Hemodynamic Study) is a prospective open-label nonrandomized clinical study of Definity in patients (16 with elevated and 16 with normal pulmonary artery pressure) during rest echocardiography. The study evaluated pulmonary hemodynamics. Adverse events, vital signs, ECGs, and laboratory measurements were also evaluated. The study conduct was good and the clinical reviewer determined that the quality of the data was acceptable.
- DMP 115-418 (Retrospective Database Study) is a retrospective study of critically ill patients. Mortality outcome data from 16223 critically ill patients (full dataset analysis) who received Definity with rest transthoracic echocardiography were compared to patients with noncontrast echocardiography using propensity scores matching techniques.

FDA and the Applicant agreed on the design of these studies. These studies were designated as postmarketing commitment or requirements and were the focus of an advisory committee meeting. The clinical and statistical reviewers in their reviews highlight several important limitations inherent in the data source and methodology of these postmarketing studies. These limitations would not permit the development of reliable estimates of the incidence of serious reactions associated with the use of Definity. Nevertheless, the clinical reviewer believes that the study results will prove useful in supporting refinement of the label with respect to information on likelihood of risk in critically ill patients, and recommendations for monitoring for adverse reactions (*see Section 8 of this review*). This assessment is generally consistent with the recommendations made by an FDA advisory committee convened to discuss the data from the PMC/PMR studies for Definity and for the other approved ultrasound contrast agent Optison manufactured by GE Healthcare (*see Section 9 of this review*). The CDTL agrees with these assessments.

2. Background

Important safety considerations

Because ultrasound contrast agents contain numerous small microspheres, there have been concerns related to microvascular obstruction. Preclinical data had shown the potential for these agents to induce pulmonary hypertension particularly in porcine models; however relevant clinical safety studies were not performed before the approval of Definity. In addition the patient population evaluated in the clinical development program of Definity did not include critically ill patients. Therefore the manufacturer agreed as a postmarketing commitment to evaluate Definity in actual clinical use. However the conduct of the study was delayed.

In 2006 and 2007, FDA became aware of a number of deaths temporally related to the administration of Definity. These deaths generally followed cardiovascular collapse or a hypersensitivity reaction and occurred predominantly in patients with underlying cardiac or pulmonary disease. Because of these findings, a number of modifications were made to the Definity label including addition of boxed warnings and new contraindications. The primary clinical reviewer (Dr. Filice) discusses in detail the labeling changes in 2007 and 2008.

To further characterize the risks involved FDA required two postmarketing clinical studies:

- A study that will utilize an existing database to compare in hospital mortality in critically ill patients undergoing echocardiography with and without the sponsor's ultrasound contrast agent.
- A clinical trial that, at a minimum, provides pulmonary hemodynamic data from at least 30 patients with known or suspected cardiac disease who are undergoing an echocardiogram with the sponsor's ultrasound contrast agent.

The applicant also agreed to perform as a postmarketing commitment:

- A study of at least 1000 patients undergoing echocardiography with the sponsor's ultrasound contrast agent in routine clinical practice.

3. CMC/Device

The supplemental application makes no changes to the drug substance, the drug product or their tests and specifications. Therefore no CMC review was necessary. No new devices are proposed for use in this application.

4. Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology data were needed and none were provided.

5. Clinical Pharmacology/Biopharmaceutics

The submission contains no new clinical pharmacology data. The FDA clinical pharmacology reviewer (Dr. John) recommended changes to the format of the clinical pharmacology section of the package insert. Dr John recommended approval of the supplement from the Clinical pharmacology perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy



(b) (4)

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8. Safety

Definity registry study

The study was adequately designed to assess potential acute adverse reactions and clinical and laboratory abnormalities. No deaths or serious adverse events were observed in 1053 patients in the prospective safety registry. Adverse events were observed overall in 11% of patients. The safety monitoring procedures did not identify subclinical abnormalities in a broader patient population than the population studied in the premarket phase. The reviewer recommends that these data be cited in the package insert and that the monitoring recommendations in the product label be lessened.

Definity studies in critically ill patients

Pulmonary Hemodynamic Study

The pulmonary hemodynamic study did not show clinically important hemodynamic changes in association with Definity. No deaths or other serious adverse events were observed in 32 patients. Only two adverse events in one patient were considered possibly related to Definity; the events were not clinically important. The clinical reviewer believes that this study fulfills the PMR and that the results can be cited in the label. For more detailed review of the pulmonary hemodynamic study, please see Dr. Filice's review.

Retrospective Database Review Study

The study was designed to compare mortality in critically ill hospitalized patients who received contrast enhanced echocardiography and critically ill patients who underwent echocardiography without contrast. The study used discharge data of hospitalized patients from Premier's Perspective database in patients with discharge data from January 1, 2002 to June 15, 2008.

The primary endpoint was 48-hour mortality defined as a discharge code of deceased on the same calendar day or day after echocardiography. The FDA statistical reviewer estimated lower mortality risk in Definity patients relative to patients who underwent echocardiography without contrast. There were 2.18% (353/16199) and 2.73% (443/16199) 48-hour deaths in the

Definity and non-contrast matched analysis groups respectively. The odds ratio (Definity to noncontrast) estimate of 48-hour mortality was 0.78, 95% CI (0.67, 0.90).

The database and methodology limitations inherent in the retrospective study have important limitations that do not allow reliance on the point estimates calculated. Nevertheless, the lack of safety signal in the study is noteworthy. The clinical reviewer believes that the study fulfills the PMR; however the limitations of the data preclude citing the data in the product label. The FDA reviewers' conclusions and recommendation are consistent with the advice the FDA received at a joint Advisory Committee meeting on May 2, 2011 (*see Section 9 of this review*).

9. Advisory Committee Meeting

On June 24, 2008, the Cardiovascular and Renal Drugs Advisory Committee met to discuss the safety of ultrasound contrast agents. The Committee endorsed the proposed risk assessment plans for the approved ultrasound contrast agents (Definity and Optison).

On May 2, 2011 the Cardiovascular and Renal Drugs and the Drug Safety and Risk management Advisory Committees met to discuss the results of the postmarketing studies for Definity and Optison and to receive a safety update for SonoVue an ultrasound contrast agent that is investigational in the US and is marketed in Europe and Asia. For the full review of the relevant data please refer to the FDA's and the Applicant's briefing packages and presentations materials¹.

Registry study. Several committee members felt the results of the safety registry were sufficiently informative to include them in labeling.

Pulmonary Hemodynamic Study. The Committee felt that the numbers of patients studied was small and that the pulmonary hypertension at baseline was not severe, but that these studies provided reasonable assurance that Definity do not cause important pulmonary hemodynamic changes. Several members of the committees felt the results of the studies could be included in the labeling.

Retrospective Database Review Study. The Committee noted that observational studies are important for assessing safety signals in the post-marketing phase, however, the databases from observational studies have important imitations (e.g. lack of precise time of or cause of death, potentially unequal matching due to hidden covariates). The results of the Applicant's study are not robust and are difficult to interpret. Members commented on the use of propensity score matching and the lack of confidence in this matching technique to appropriately balance the different groups. The committee felt that the observational study data

¹ <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm250295.htm>

should not be included in the labeling based on the designs of the studies and the limitations of the results.

10. Pediatrics



11. Other Relevant Regulatory Issues

Consultations on pediatric and maternal health labeling

- The FDA maternal health team consultant (Dr. Bhatnagar) recommended adding to the label (Section 8.3 Nursing Mothers) a recommendation to pump and discard breast milk once after dosing because of the rapid clearance of the drug. The CTDL agrees with this recommendation.



Consultation on QT prolongation

The FDA consultant from the Division of Cardiorrenal Drugs (Dr. Balakrishnan) evaluated the potential for QTc prolongation. The consultant reviewed the Definity label and the following two study reports.

The Definity label reports ECG interval data in 221 study subjects at time points from 1 to 72 hours after Definity bolus injection. QTc prolongations of >30 msec were noted in 64 (29%) subjects. Forty-six out of 64 subjects with QTc prolongations were further evaluated and 39% (18/46) showed associated cardiac rhythm changes. The consultant states that these findings are inconclusive because the ECGs were not obtained at the Tmax for Definity. In addition to be more informative the label needs to capture outliers with absolute change over 500 ms or over 60 ms change from baseline.

In study DMP 115-416 32 patients, 16 with normal pulmonary pressures and 16 with pulmonary hypertension underwent a resting echocardiogram with Definity along with pulmonary arterial catheterization; 12-lead ECGs were obtained before the echocardiogram and 2 hours+ 52 minutes after administration. Multiple intervals were measured (PR, RR, QRS, QT, and QTcB). The Applicant concluded that no clinically significant changes are seen in association with Definity administration.

The active moiety of Definity (octafluoropropane) declines monoexponentially after intravenous administration with a mean half-life of 1.3 minutes. The consultant found the ECG data to be inconclusive because the ECGs were not collected at Tmax (30-40 seconds post-dose), and even large ECG effects could not be excluded. Also in general single ECGs were recorded with no central over-read, therefore the values reported were not considered reliable.

The consultant took into account the short half-life of Definity, its use in monitored patients under supervision by personnel trained in arrhythmia management. Based on these considerations the consultant did not feel that a TQT study to quantify QT effects of Definity is required.

The CDTL agrees with these conclusions. The new data provided are inconclusive and do not need to be added to the label. The existing information in the present label seems to suggest a greater level of concern than warranted by the evidence. It might be useful to reevaluate the data from the 221 patient experience and to cite the numbers of patients with QTc absolute change >500 ms or over 60 ms from baseline as recommended by the consultant.

Financial disclosures/audits

Two investigators in study 415 and one investigator in study 415 and 416 reported payments greater than \$25,000 for honoraria during the course of the studies. Approximately 15% of patients in study 415 and no patients in study 416 were enrolled by these investigators. These reports do not raise concerns about the integrity of the studies.

12. Labeling

The efficacy supplement triggered the revision of the package insert in Physician Labeling format. The Applicant proposed several efficacy and safety labeling changes (*see Section 1 of this review*). FDA communicated to the Applicant the following labeling comments:

-  (b) (4)
- It is reasonable to remove the cautionary statement about stress testing from the Indications and Usage section of the label.
- The Boxed warning needs to be reinstated. New information about the incidence of severe reactions could be added. The requirements for monitoring could be lessened.
- Data from the prospective safety registry and the pulmonary hemodynamic study are appropriate for inclusion in the label. However data from the retrospective

observational study should not be included because of the important methodological concerns discussed by FDA at the advisory committee meeting.

- [REDACTED] (b) (4)

FDA communicated to the Applicant the specific labeling language recommended. FDA and the Applicant did not reach agreement on the labeling. This lack of agreement led to the FDA decision to take a complete response action on the present supplemental application.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

[REDACTED] (b) (4)

In addition the FDA reviewers did not agree with the Applicant regarding the overall interpretation of the PMC/PMR study results. For these reasons the clinical reviewer recommends a complete response action for this efficacy supplement and the CDTL agrees with this recommendation.

- Risk Benefit Assessment

The CDTL agrees with Dr. Filice that the overall risk benefit profile for Definity for the approved use remains favorable.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None are needed.

- Recommendation for other Postmarketing Requirements and Commitments

None are needed. Subsequent to the FDA clinical and statistical reviews of the complete reports of the Definity PMC/PMR studies, the CDTL recommends that the PMC/PMR be declared fulfilled.

- Recommended Comments to Applicant

[REDACTED] (b) (4)

[Redacted content]

(b) (4)

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/s/

LIBERO L MARZELLA
07/28/2011

DIVISION OF MEDICAL IMAGING PRODUCTS

Clinical Review Memorandum

Date: December 10, 2010
Sponsor: Lantheus Medical Imaging
Product: Definity (perflutren)
Regulatory submission: NDA-21064
Supporting Document: 204
Reviewer: Ross Filice, M.D. DMIP/ODE IV/CDER

Background

The sponsor has submitted [redacted] (b) (4)
[redacted] as well as modifying current safety warnings. [redacted] (b) (4)

Findings and Regulatory Action

[redacted] (b) (4)

This information and request was included in the 74-day letter sent on December 10, 2010.

References

1. [redacted] (b) (4)
2. [redacted]

3.

4.

5.

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/s/

ROSS W FILICE
12/10/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21064

Applicant: Lantheus

Stamp Date: 09/29/2010

Drug Name: Definity (perflutren) NDA/BLA Type: sNDA

Major proposed labeling changes

(b) (4)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Studies Submitted in Support of Changes (see appendix for details)

Efficacy Changes



(b) (4)

Safety Changes

4 trials are submitted in support of the proposed safety changes. 3 of these are from the Postmarketing Requirements that arose after the Advisory Committee meeting in 2008. These include a retrospective database review of critically ill patients who received Definity, a prospective registry of patients in typical clinical practice who received Definity, and a small prospective evaluation of pulmonary hemodynamics in patients with and without pulmonary hypertension. (b) (4)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			(b) (4) presents QT interval analysis.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		X		(b) (4) individual study protocols exist, but reports are not provided, thus no narrative summaries provided for these individual trials.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			(b) (4)
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow	X			Datasets: (b) (4)

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	reasonable review of the patient data?				415, 416, (b) (4), (b) (4) Reviews: (b) (4) 418
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			(b) (4), 416, 415, (b) (4)
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Provide complete study reports including demographics, narrative results, tabular results, and complete datasets for each of (b) (4). Also provide complete safety data and analysis including narrative summaries of any deaths, serious adverse events, or dropouts. These trials are:

(b) (4)

2. Provide subgroup analysis of efficacy and safety by age, gender, and racial subgroups for all trials except literature reviews [21 CFR 314.50(d)(5)(v)]. This has already been done for DMP 115-418, but otherwise appears incomplete or absent in the remaining trials. Please provide this analysis, or justification for exclusion, for the following trials:

(b) (4)

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

d. DMP 115-416

e. DMP 115-415

f.  (b) (4)

and for the following  (b) (4)

 (b) (4)

3. Provide a signed statement of Good Clinical Practice that states that all clinical studies were performed under the supervision of an IRB and with adequate informed consent procedures.

Ross Filice, M.D.	11/17/2010
_____ Reviewing Medical Officer	_____ Date

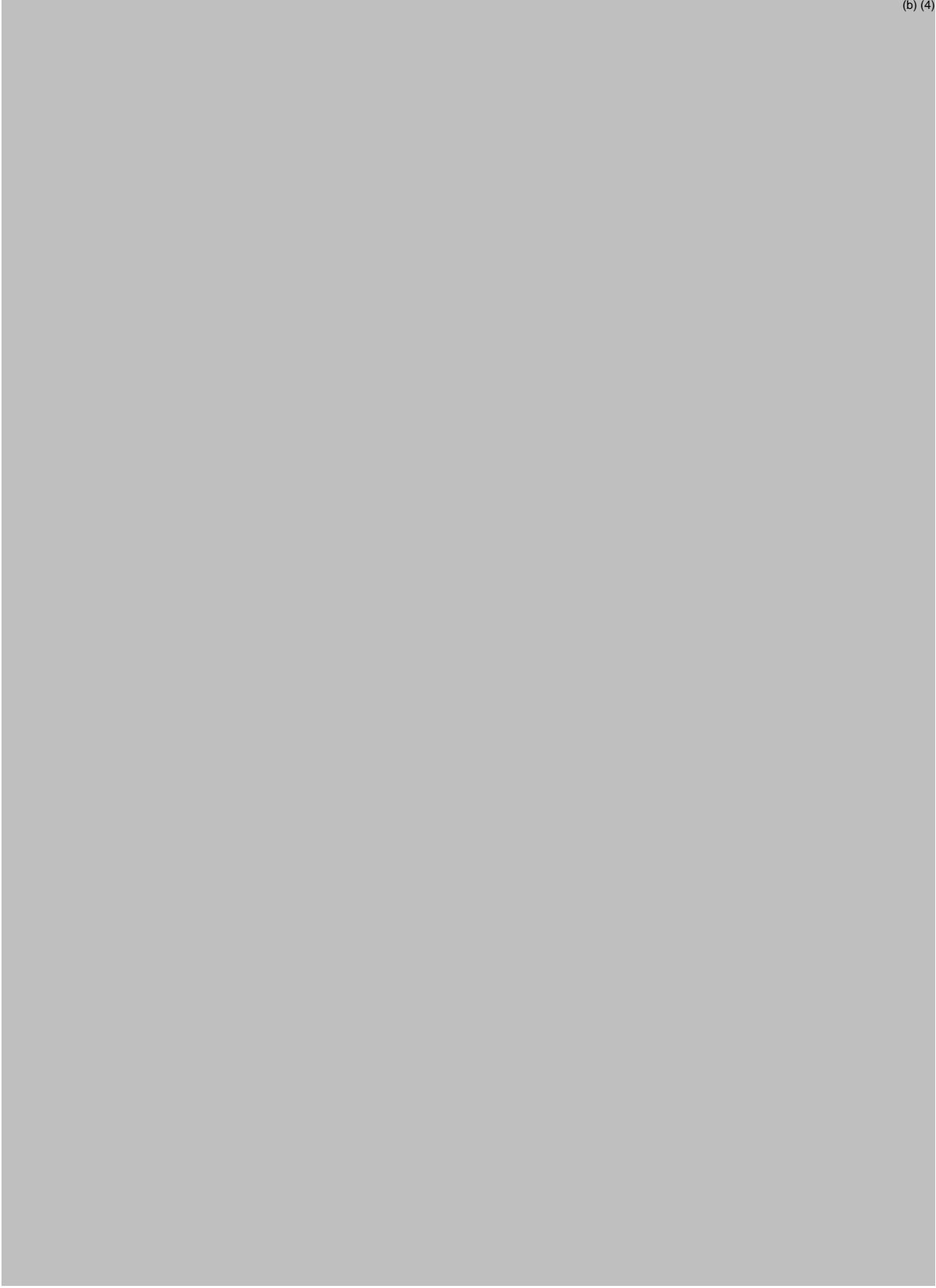
Louis Marzella, M.D.	11/17/2010
_____ Clinical Team Leader	_____ Date

Appendix - Submitted Clinical Trials

 (b) (4)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

(b) (4)



File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 2871527

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

(b) (4)

Safety Changes

1. DMP 115-416

- prospective open-label trial - 16 pts with pulmonary hypertension (PASP > 35 mmHg), 16 controls
- primary endpoint: pulmonary artery hemodynamics (many parameters)
- secondary endpoint: SAE, AE, immunology parameters, labs, vital signs, physical exams, ECGs
- no prospective statistical evaluation defined, post-hoc comparisons were 2-sided, 5% error, Wilcoxon Rank sum test
- Conclusion: no statistically or clinically significant changes in parameters

2. DMP 115-415

- prospective open-label surveillance registry for safety, Feb 2008-Apr 2009
- population: 1053 patients with suboptimal echocardiograms, regular clinical practice, not critically ill, some rest some stress
- primary endpoint: death or life-threatening events within 30 minutes of Definity
- secondary endpoint: SAE and AE up to 24 hrs after Definity, monitoring parameters (vital signs, ECG, oxygen sat) up to 30 minutes after Definity
- 10.8% treatment emergent AE (4.5% rest, 13% stress)
- 13% AE at rest, 27.7% AE stress
- no deaths or SAE

3. DMP 115-418

- retrospective database review of 1000 patients with propensity score matching
- primary endpoint: 48 hour mortality
- secondary endpoint: all cause in-hospital mortality, acuity of illness and prior risk of mortality, subgroup analysis of 48 hour mortality
- Conclusion: mortality benefit in Definity group (2.14% death in Definity, 3.09% death in non-contrast, OR: 0.686 [0.596-0.789])

(b) (4)

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/s/

ROSS W FILICE
12/02/2010

LIBERO L MARZELLA
12/03/2010

DIVISION OF MEDICAL IMAGING PRODUCTS
Medical Officer Review of a Post Marketing Requirement

IND: 48,626 (271); received 03/30/2009
NDA: 21064 (SD 203); received 09/29/2010
Product: Definity (Perflutren)
Sponsor: Lantheus Medical Imaging

(b) (4)



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

/s/

MICHELE B FEDOWITZ
11/23/2010

LIBERO L MARZELLA
11/23/2010