

Advisory Committee Briefing Document

Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Title: DEFINITY® Advisory Committee Briefing Document
Product: DEFINITY® (Perflutren Lipid Microsphere)
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EXECUTIVE SUMMARY

DEFINITY® is a microbubble contrast agent “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.” This document summarizes clinical trials, published literature, and post-marketing experience since the last Advisory Committee meeting in June 2008.

DEFINITY® has been commercially available in the US since its approval in July 2001 and is the most widely used echocardiography contrast agent with approximately 95% of the current market. A class Boxed Warning and several contraindications were added in October 2007 by the FDA in response to the identification of 4 fatal adverse events (AEs) that occurred within 30 minutes of the use of DEFINITY®. This new Boxed Warning also called for monitoring of all patients for at least 30 minutes after administration of DEFINITY®.

After review of additional data submitted by Lantheus Medical Imaging, Inc. (LMI) and other microbubble manufacturers, the contraindications were removed in May 2008 and monitoring of patients was limited to those with unstable cardiopulmonary conditions and those with pulmonary hypertension. Three post-marketing studies were required to further evaluate safety in general clinical use and in special populations of patients with either pulmonary hypertension and/or critical illness. Lantheus completed these studies and submitted written reports within the requested timeframe.

The first multicenter study (DMP 115-415) prospectively evaluated the nature and rate of adverse reactions in an open registry of patients administered DEFINITY® for routine clinical care. In 1053 patients, the majority of whom had underlying cardiac and/or pulmonary disease, there were no deaths or serious adverse events (SAEs). Minor transient AEs were similar in nature and frequency to those seen historically. During and for 30 minutes after DEFINITY® administration, there was no evidence of clinically significant changes in vital signs, electrocardiograms, and oxygen saturation measurements.

The second study (DMP 115-416) prospectively evaluated safety in patients with or without baseline pulmonary hypertension who were undergoing clinically indicated right-heart invasive catheterization. All patients (N=32) received the maximum dose of DEFINITY® per product labeling, and there were no significant changes in right- or left-sided pressures in patients with or without pulmonary hypertension. There were no deaths, no SAEs, and minor transient AEs were similar in each group. These results are consistent with an independent published study.¹

The third study (DMP 115-418) retrospectively evaluated all-cause mortality within 48 hours and all-cause mortality throughout the hospital stay in critically ill patients using validated data from the Premier Perspective™ database. Records from over 500 hospitals and over

1 million cases were evaluated. Propensity matching based on patient demographics and 23 clinical conditions was used to develop case and control groups exposed to DEFINITY[®] and those undergoing echocardiography without contrast. The observed 48-hour mortality was 32% lower in the DEFINITY[®] group than in the noncontrast group. Furthermore, the lower risk of mortality in the DEFINITY[®] group was preserved at hospital discharge. Both results were highly statistically significant. Subgroups with pulmonary hypertension or acute cardiac or pulmonary conditions were similarly at lower risk of death in the DEFINITY[®] group than in the noncontrast group.

The DMP 115-418 study was not designed to answer mechanistic questions about the DEFINITY[®]-related survival advantage. However, the improved survival may be the consequence of improved clinical decision making, based on improvement in left ventricular opacification and endocardial border delineation with DEFINITY[®], and the association between improved imaging and changes in patient management.^{2,3}

The DMP 115-418 findings are also supported by a recent independent meta-analysis⁴ of 8 studies that collected data on mortality and myocardial infarction (MI), which found that the use of contrast was associated with a decreased mortality rate and MI rate in hospitalized patients undergoing echocardiography. This meta-analysis provides further evidence that use of contrast-enhanced echocardiography ultrasound is safe in hospitalized patients.

LMI proactively seeks safety information from health care providers by including 800- and local numbers on all prescribing information and by providing clearly identified AE reporting phone, fax, and e-mail contacts on the DEFINITY[®] product website. Detailed AE case information gathered through the LMI pharmacovigilance system indicates that some of these events may result directly from concomitant medications (including pharmacologic stress agents) and progression of underlying serious illness (ie, pseudo-complications^{5,6}). Rarely, SAEs appear to have an allergic component.

No subgroup of patients appears to be at particular risk for these serious events. Current rates of these adverse reactions are similar to the rates that were reported prior to the 2007 Boxed Warning. An independent safety Data Monitoring Committee (DMC) has convened twice for periodic DEFINITY[®] safety data review from all available sources. The DMC concluded that no additional safety risks have emerged since 2008.

Following implementation of the Boxed Warning, utilization of DEFINITY[®] has been significantly reduced, possibly in cases where contrast administration would be considered appropriate or even necessary for accurate and immediate medical diagnosis. Current utilization rates are ~1.5%, which is well below the estimated frequency of suboptimal echocardiograms in the US (15% to 20%). Current use is also less than what would be expected if professional society-based guidelines, accreditation standards, and clinical use consensus statements were followed (~ 15%, higher in the intensive care unit setting).⁷⁻⁹ In

some cases, patients may have undergone alternative imaging procedures that are associated with rates of SAEs and mortality that exceed the rates associated with ultrasound contrast echocardiography.¹⁰

Lantheus believes that new data obtained from clinical trials and post-market surveillance continue to demonstrate a favorable benefit-risk profile. Lantheus believes that the risks of DEFINITY® are well characterized and that the product offers an advantageous imaging modality that is immediately available at point-of-care for diagnosis and does not expose patients to ionizing radiation.

Based on a stable safety profile and results from post-market safety studies conducted in patients with serious comorbidities, as outlined above, Lantheus believes the use of a box warning should be reconsidered.

TABLE OF CONTENTS

EXECUTIVE SUMMARY	2
TABLE OF CONTENTS	5
LIST OF IN-TEXT TABLES	7
LIST OF IN-TEXT FIGURES.....	8
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	9
1 INTRODUCTION.....	11
2 REGULATORY SUMMARY	14
2.1 Product Characteristics.....	14
2.2 Regulatory Milestones	14
2.3 Boxed Warning.....	14
2.4 Advisory Committee Meeting	15
3 SUMMARY OF PRECLINICAL AND CLINICAL DATA PRESENTED TO THE 2008 ADVISORY COMMITTEE.....	15
3.1 Preclinical.....	16
3.2 Clinical.....	16
4 POST-MARKETING COMMITMENTS FULFILLED SINCE PREVIOUS ADVISORY COMMITTEE	18
4.1 Clinical Studies.....	19
4.1.1 DMP 115-415 Safety Registry in Routine Clinical Practice	19
4.1.1.1 Demographic and Baseline Characteristics in DMP 115-415 Safety Registry in Routine Clinical Practice.....	19
4.1.1.2 Patient Exposure to DEFINITY® in DMP 115-415 Safety Registry in Routine Clinical Practice.....	24
4.1.1.3 Safety Data From DMP 115-415 Safety Registry in Routine Clinical Practice.....	24
4.1.1.4 Summary of DMP 115-415 Safety Registry in Routine Clinical Practice.....	27
4.1.2 DMP 115-416 in Patients With Elevated Pulmonary Artery Systolic Pressure.....	27
4.1.2.1 Demographic and Baseline Characteristics in DMP 115-416 Patients With Normal or Elevated Pulmonary Artery Systolic Pressure	27
4.1.2.2 Patient Exposure to DEFINITY® in DMP 115-416 Patients With Normal or Elevated Pulmonary Artery Systolic Pressure.....	29

4.1.2.3	Pulmonary Artery Hemodynamic Data From DMP 115-416 in Patients With Normal or Elevated Pulmonary Artery Systolic Pressure	29
4.1.2.4	Adverse Event Data From DMP 115-416 in Patients With Normal or Elevated Pulmonary Artery Systolic Pressure	32
4.1.2.5	Summary of DMP 115-416 in Patients With Elevated or Normal Pulmonary Artery Systolic Pressure	33
4.1.3	DMP 115-418 Retrospective Database Study in Critically Ill Patients.....	33
4.1.3.1	Demographic and Baseline Characteristics in DMP 115-418 Retrospective Study in Critically Ill Patients	34
4.1.3.2	Analyses of Mortality in DMP 115-418 Retrospective Study in Critically Ill Patients	37
4.1.3.3	Summary of DMP 115-418 Retrospective Study in Critically Ill Patients	40
4.1.4	Conclusions Based on Clinical Studies	40
5	LITERATURE REVIEW	41
5.1	Individual Publications.....	41
5.2	Meta-Analysis Publications.....	42
5.3	Literature Conclusions	48
6	SUMMARY OF POST-MARKETING DATA.....	49
6.1	Product Distribution.....	49
6.2	Safety Surveillance Methods and Process: Overview.....	49
6.2.1	Summary.....	49
6.2.2	Training/Awareness of Adverse Event Reporting Requirements	50
6.2.3	Adverse Event Processing	50
6.2.4	Medical Literature Review	50
6.2.5	Safety Signal Detection	50
6.2.6	Post-Marketing Data Monitoring Committee	51
6.2.7	Education of Health Care Providers	51
6.2.8	Aggregate Safety Reporting.....	51
6.3	Safety Surveillance: Results	51
6.3.1	Adverse Events/Reactions	51
6.3.2	Overall Post-Marketing Experience	52
6.3.3	Important Identified Risks	55
6.3.3.1	Serious Cardiopulmonary Reactions (SCPRs).....	55

6.3.3.2	Hypersensitivity and Anaphylactic/Anaphylactoid and Hypersensitivity Reactions.....	57
6.3.4	Convulsions.....	60
6.3.5	Events with a Fatal Outcome (15 April 2008 to 08 Mar 2011)	60
6.4	Data Monitoring Committee (DMC)	67
6.5	Lantheus Signal Detection Activities.....	68
7	OVERALL CONCLUSIONS	74
8	LITERATURE CITED	77

LIST OF IN-TEXT TABLES

Table 4-1	Demographic and Baseline Characteristics of Patients in the Safety Registry Study who Received DEFINITY® in Routine Clinical Practice (DMP 115-415).....	20
Table 4-2	Cardiac Medical History of Patients in the Safety Registry Study who Received DEFINITY® in Routine Clinical Practice (DMP 115-415) (N [%]).....	22
Table 4-3	Pulmonary Medical History of Patients in the Safety Registry Study who Received DEFINITY® in Routine Clinical Practice (DMP 115-415) (N [%]).....	23
Table 4-4	Treatment-Emergent Adverse Events ($\geq 0.5\%$) in Patients in the Safety Registry Study who Received DEFINITY® in Routine Clinical Practice (DMP 115-415) (N [%]).....	25
Table 4-5	Demographic and Baseline Characteristics in DMP 115-416 Patients With Normal or Elevated Pulmonary Artery Systolic Pressure	28
Table 4-6	Cardiac Medical History of Patients Enrolled in the Study of Elevated Pulmonary Artery Systolic Pressure (DMP 115-416) (N [%]).....	29
Table 4-7	Analyses of Change From Baseline of Hemodynamic Measurements in Patients Enrolled in the Study of Elevated Pulmonary Artery Systolic Pressure (DMP 115-416).....	31
Table 4-8	Adverse Events Reported in Patients with Normal and Elevated Pulmonary Artery Systolic Pressure (DMP 115-416).....	33
Table 4-9	Selected Patient Demographic Characteristics in the Matched Dataset of the Retrospective Database Study of Critically Ill Patients (DMP 115-418).....	35
Table 4-10	Frequencies of 23 Comorbid Conditions in Patients in the Matched Dataset of the Retrospective Database Study of Critically Ill Patients (DMP 115-418).....	36

Table 4-11	Comparison of 48-Hour Mortality in DMP 115-418 for Critically Ill Patients with Noncontrast or DEFINITY® Echocardiography (Matched Dataset).....	37
Table 4-12	Comparison of Hospital Stay, All-Cause Mortality in DMP 115-418 for Critically Ill Patients with Noncontrast or DEFINITY® Echocardiography (Matched Dataset).....	38
Table 4-13	Comparison of 48-Hour Mortality for Critically Ill Patients with Noncontrast or DEFINITY® Echocardiography by Major Comorbidity (Matched) (DMP 115-418).....	39
Table 5-1	Table of Relevant DEFINITY® Publications	44
Table 6-1	Foreign Marketing of DEFINITY®	49
Table 6-2	All Adverse Events Reported During Post-Marketing Experience (28 Dec 2007 – 27 Dec 2010) in Each System Organ Class	53
Table 6-3	Serious Adverse Events Reported During the Post-Marketing Experience (28 Dec 2007-27 Dec 2010) by Preferred Term.....	53
Table 6-4	Most Frequently Reported Nonserious Adverse Events by Preferred Term During Post-Marketing Experience (28 Dec 2007 - 27 Dec 2010)	54
Table 6-5	Terms for Serious Cardiopulmonary Reactions Reported During Post-Marketing Experience (28 Dec 2007 - 27 Dec 2010)	56
Table 6-6	All Serious Hypersensitivity, Anaphylactic, and Anaphylactoid Reactions Reported During Post-Marketing Experience (28 Dec 2007 – 27 Dec 2010) by Preferred Term	58
Table 6-7	Serious Events in the Convulsion SMQ During Post-Marketing Experience (28 Dec 2007 - 27 Dec 2010) by Preferred Term.....	60
Table 6-8	Events With a Fatal Outcome During the Interval 15 Apr 2008 - 08 Mar 2011	62

LIST OF IN-TEXT FIGURES

Figure 6-1	Fatal Post-Marketing Cases Within 30 Minutes of DEFINITY® Administration by Quarter.....	69
Figure 6-2	Serious Case Rate Difference From Mean by Quarter.....	70
Figure 6-3	Serious Anaphylactic Reaction Case Rate Difference From Mean by Quarter	71
Figure 6-4	Serious Events in the Convulsion SMQ Case Rate Difference From Mean by Quarter	72
Figure 6-5	Serious Cardiopulmonary Reactions and Fatal Case Rate Difference From Mean by Quarter	73

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event(s) of special interest
ASE	American Society of Echocardiography
APR-DRG	All Payer Refined – Diagnosis Related Group
CABG	coronary artery by-pass graft
CAD	coronary artery disease
CARPA	complement activation-related pseudoallergy
CE	contrast echocardiography
CHF	congestive heart failure
CI	confidence interval
CO	cardiac output
COPD	chronic obstructive pulmonary disease
DMC	Data Monitoring Committee
DMP 115	perflutren (lab code)
DSE	dobutamine stress echocardiography
ECG	electrocardiogram
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GPV	global pharmacovigilance
ICAEL	Intersocietal Commission for Accreditation of Echocardiography Laboratories
ICU	intensive care unit
ICSR	Individual Case Safety Report
IST	investigator-sponsored trial
IV	intravenous

LMI	Lantheus Medical Imaging
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarct/infarction
MSRT	Medical Safety Review Team
NCE	noncontrast echocardiography
PASP	pulmonary artery systolic pressure
PCI	percutaneous coronary intervention
PADER	Periodic Adverse Drug Event Report
PADP	pulmonary artery diastolic pressure
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PFP	perfluoropropane, also known as perflutren
PSUR	Periodic Safety Update Report
PV	pharmacovigilance
RAP	right arterial pressure
SAE	serious adverse event
SCPR	serious cardiopulmonary reaction
SD	standard deviation
SDEA	Safety Data Exchange Agreement
SMQ	Standard MedDRA Query
SPECT	single photon emission computed tomography
TGA	Therapeutic Goods Administration
TTE	transthoracic echocardiogram
US	United States

1 INTRODUCTION

In spite of improving survival trends, coronary heart disease (CHD) is the number one cause of death in the United States (US), leading to 425,425 deaths in 2006.¹¹ Furthermore, an estimated 1.2 million myocardial infarcts (MIs) occurred in 2006, of which 141,462 were fatal. Also, congestive heart failure (CHF) rates continue to increase as the population ages and as therapies for acute cardiac syndromes reduce mortality. Echocardiography is widely used for the diagnosis and management of these and other cardiopulmonary conditions.

Echocardiography is a practical, cost-effective, and noninvasive imaging modality that has been used for over 30 years as the diagnostic procedure of choice for a wide variety of cardiac and vascular diseases, including the detection of coronary artery disease (CAD). However, physical factors limit the quality of left ventricular images in up to 10 to 20% of patients, especially those with obesity, lung disease, and bodily structural abnormalities.^{7, 12-14} Many times these patients are seriously ill or in critical care. In stress echocardiography, the proportion of technically limited studies may be as high as 33%.¹⁵ Poor images reduce the sensitivity and specificity of the tests and thus impair the quality of the diagnostic information obtained.

In response to these issues, echocardiography contrast agents were developed to provide greater left ventricular opacification and delineation of the left ventricular endocardial borders, so that the size, shape, and motion of the ventricular walls can be better visualized. Because of the physics of ultrasound scattering, the contrast agents developed have generally been in the form of short-lived gas-filled microbubbles that are sufficiently small to pass through the pulmonary capillaries and therefore appear in the left side of the heart after simple intravenous (IV) bolus injection or infusions. Microbubble contrast agents have been available in the US since the first approved agent in 1994 (Albunex® MBI, California).

So-called “second generation” perfluorocarbon-filled microbubble agents DEFINITY® (Lantheus Medical Imaging, Inc., MA) and OPTISON™ (GE Healthcare, UK) were approved by the US Food and Drug Administration (FDA) after demonstrating superiority to placebo and Albunex®, respectively.¹⁶ In addition, both agents demonstrated acceptable safety profiles. These agents have greater bubble uniformity and longer intravascular persistence, with resulting improvements in echocardiographic images.¹⁷

According to internal sales data, approximately 2.9 million patients have received DEFINITY® contrast-enhanced echocardiography procedures since the first product approval in the year 2000 (Canada). Regulatory milestones in the US are discussed in [Section 2](#).

The American Society of Echocardiography (ASE) has developed comprehensive guidelines for the use of contrast in echocardiography procedures. Some of these guidelines include:

- “Guidelines for the Cardiac Sonographer in the Performance of Contrast Echocardiography: Recommendations of the American Society of Echocardiography Council on Cardiac Sonography”⁸
- “American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography”⁷
- “Stress Echocardiography: Recommendations for Performance and Interpretation of Stress Echocardiography”¹⁸

These guidelines are useful in communicating the safe and effective use of contrast echocardiography. They recognize that contrast is a necessary option for the diagnosis of patients with cardiac disease, since it provides important information for difficult-to-image patients and provides a portable bedside option for critically ill patients.

In 2010, the Intersocietal Commission for Accreditation of Echocardiography Laboratories (ICAEL) revised its standard for accreditation to include requirements around contrast utilization.⁹ In the current standard, contrast is indicated when 2 contiguous segments are not visualized and the standard further specifies that, if contrast is not used, the laboratory must have a written policy for alternative imaging. The standard also specifies that contrast should be used for quantification of cardiac chamber dimensions, volumes, ejection fraction, and assessment of regional wall motion.

As noted above, the most frequent causes for nonevaluable procedures resulting from poor quality images are patient obesity, lung disease, and bodily structural abnormalities, as well as difficulties in imaging associated with emergency or critical care situations. Moreover, it is worth noting that practitioners are instructed to utilize microbubble contrast agents when baseline images are suboptimal (> 2 endocardial segments poorly visualized), when, as a standard of care, contrast salvages otherwise nondiagnostic procedures.¹⁹ Contrast allows these otherwise nonevaluable patients to benefit from the diagnostic information obtained from a noninvasive standard-of-care procedure without requiring further risk, whether from exposure to radiation during nuclear testing, gadolinium-containing agents, iodinated contrast agents, or invasive coronary angiography procedures.¹⁹ In addition, the expense of other testing - in time and procedural costs - is avoided when a contrast echocardiography procedure provides the desired diagnostic information.

As an example of the benefits that can accrue from use of contrast, Kurt et al reported on a prospective study of patients with technically difficult echocardiographic studies who received DEFINITY® as part of routine clinical diagnostic care,³ according to the ASE Consensus Statement recommendations for use.⁷ The authors found that, after DEFINITY® echocardiography, the percent of uninterpretable studies decreased significantly and use of DEFINITY® was associated with a significant increase in the mean number of endocardial wall segments visualized. Improvements in information available for clinical

decision-making led to additional diagnostic tests being avoided in 32.8% of patients and an overall change in management in 35.6% of patients. The effect of contrast increased with worsening quality of the unenhanced study, especially in intensive care units (ICUs) among critically ill patients. This had a significant impact on patient management decisions.

Contrast echocardiography procedures are especially useful in critically ill patients, where the clinical setting mandates the efficient and timely acquisition of diagnostic patient information. At times, it is the only possible approach, as patients who are too sick to undergo invasive radiological studies, computed tomography, or magnetic resonance imaging can undergo contrast echocardiography. In these sick patients, clinical assessments include an immediate point-of-care evaluation of hypotension, shock, post-cardiac-arrest status, and tamponade.^{16, 17}

However, this appropriate practice pattern may have led to some of the concerns regarding product safety. As noted by Main et al in 2007,¹⁶ complications may occur after any medical procedure and may be either attributable to the procedure itself or may be due to progression of the underlying disease state. This phenomenon has been defined as pseudo-complication and was first characterized decades ago in evaluating patient safety before and after cardiac catheterization.^{5, 6} In essence, the patients are “sick enough” to have events, including death, independent of any associated procedures. A key question becomes how to differentiate between events that are merely temporally related to the procedure and those caused by the procedure.

Nevertheless, even fully discounting the impact of pseudo-complication and comparing contrast echocardiography with other common procedures, contrast echocardiography has the most favorable benefit-risk result. For example, Main et al¹⁶ note that if the 4 fatalities reported in the FDA Alert (October, 2007) were attributable to contrast, the reporting death risk would be 1:500,000. By comparison, the mortality rate for diagnostic coronary angiography is approximately 1:1,000 and the risk of MI or death with exercise treadmill testing is approximately 1:2,500. Furthermore, the lifetime risk of fatal malignancy after single photon emission computed tomography (SPECT) imaging is estimated to be between 1:1,000 and 1:10,000.¹⁶

To summarize, contrast echocardiography is an important diagnostic tool that provides critical patient information in a cost-effective manner and avoids subjecting patients to other procedures with greater risk.^{16, 17}

2 REGULATORY SUMMARY

2.1 Product Characteristics

DEFINITY[®] is a second-generation lipid encapsulated perfluoropropane (PFP) filled microsphere suspension designed for IV administration. The product is provided in vials that contain a blend of 3 endogenous lipids (one conjugated to methoxypolyethylene glycol 5000) and PFP in the headspace. Upon activation by agitation with a Vialmix[®] (specialized mixer), the clear colorless liquid becomes a homogenous, opaque, milky white injectable suspension of PFP lipid microspheres of consistent number and size distribution. At the recommended maximum clinical dose for ultrasound imaging (0.01 mL/kg with possible administration of a second dose of 0.01 mL/kg), the average number of microspheres that are administered is low (~109 to a 70-kg individual: about the same as the number of cells in 1 mL of blood). The total amount of PFP administered at the clinical dose of activated DEFINITY[®] is small ($\leq 350 \mu\text{L}$ to a 70-kg individual).

2.2 Regulatory Milestones

A New Drug Application (NDA) was filed for DEFINITY[®] on 08 December 1998.

DEFINITY[®] received approval from the Agency on 31 July 2001. It was approved with the following indication: “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.”²⁰

2.3 Boxed Warning

The FDA raised safety concerns regarding the class of microbubble contrast agents in 2007, in part as the result of spontaneous reports of a total of 4 SAEs with fatal outcomes within 30 minutes of administration of DEFINITY[®], out of almost 2 million doses. Given the brief vascular half-life of DEFINITY[®] (1.3 minutes in normal subjects), it is improbable that events outside this window would be related to DEFINITY[®] administration. Detailed review of the 4 cases indicated that all were critically ill and that the cause of death was not certainly attributable to DEFINITY[®].

On 10 October 2007, FDA approved a required labeling supplement that included the addition of a boxed warning, additional contraindications, and warnings. In May 2008, the Agency approved revisions to the DEFINITY[®] Package Insert. This approval included revisions to the boxed warning and warning sections that focused the monitoring of patients on those with unstable cardiopulmonary conditions and pulmonary hypertension. In

addition, the contraindications that were included in the 10 October 2007 labeling supplement approval that focused on specific patient characteristics were removed.

The revisions to the Package Insert in both the October 2007 and May 2008 submissions were class changes to all perflutren-containing microsphere agents.

In addition to the label revisions, LMI committed to conducting 3 post-marketing studies:

1. a safety registry study in at least 1000 patients using DEFINITY[®] in routine clinical practice, as it is actually used in the clinical setting
2. a study to evaluate the effects of DEFINITY[®]-enhanced echocardiography on pulmonary artery hemodynamics in at least 30 patients with known or suspected cardiac disease. At least 15 of these patients were to have pulmonary artery hypertension documented on baseline pulmonary artery pressure (PAP) assessment
3. an observational clinical study using an existing database(s) to compare in-hospital mortality in critically ill patients undergoing echocardiography with and without DEFINITY[®].

Lantheus also committed to developing an independent Data Monitoring Committee (DMC) to review product safety information from all sources on a periodic and immediate basis, based on the nature of the individual reports.

2.4 Advisory Committee Meeting

On 24 June 2008, LMI participated in a joint Cardiovascular and Renal and Drug Safety and Risk Management Advisory Committee Meeting along with 2 other sponsors (GE Healthcare and Bracco).

The information presented at that meeting included DEFINITY[®] nonclinical study data, LMI-sponsored clinical trial data, a review of recent publications, and post-marketing surveillance data. The outcome from the Advisory Committee yielded no further changes to the prescribing information.

Lantheus has been invited to participate at a follow-up meeting to discuss the results of the 3 post-marketing safety studies and the interval US and international post-marketing surveillance data. This meeting will be held on 02 May 2011.

3 SUMMARY OF PRECLINICAL AND CLINICAL DATA PRESENTED TO THE 2008 ADVISORY COMMITTEE

Extensive preclinical and clinical safety and efficacy assessments established that DEFINITY[®] was effective and safe as an ultrasound contrast agent. The product was

approved in the US for left ventricular opacification and delineation of the left ventricular endocardial borders in 2001.

3.1 Preclinical

Safety pharmacology and toxicology studies were designed to support the clinical use of DEFINITY[®] as an intravenously administered agent used in the acute setting. Safety pharmacology studies in the dog demonstrated that doses up to 25 times the clinical dose (0.5 mL/kg) did not affect cardiopulmonary function. At higher doses, marked increases in respiration rate and pulmonary arterial pressure were observed and fatalities were produced. However, even in a model where severe pulmonary compromise was induced, the highest dose tested (0.2 mL/kg [10 times the clinical dose]) did not affect cardiopulmonary function.

Similarly, DEFINITY[®] (0.5 mL/kg) did not affect cardiopulmonary function in mechanically ventilated dogs. Examination of the effect of activated DEFINITY[®] on microcirculation indicated that a very small fraction (1.2%) of the administered dose was retained and this transient retention did not have a detrimental effect on systemic hemodynamics, even at 40 times the clinical dose (800 µl/kg). The safety of activated DEFINITY[®] was also demonstrated in the rhesus monkey, where cardiovascular and electrocardiogram (ECG) effects were not seen even at 50 times the clinical dose (1000 µl/kg). Studies with DEFINITY[®] in the cynomolgus monkeys also suggest that cardiopulmonary effects are only produced at very high doses levels (\geq 150-fold higher than the recommended clinical dose). The main toxicological findings in rats and cynomolgus monkeys relevant to clinical use were acute clinical signs seen with high dose levels. These were consistent with safety pharmacology studies and suggestive of a cardiopulmonary origin. In cynomolgus monkeys, clinical signs were not associated with an anaphylactoid response mediated by mast cell degranulation or activation of complement, suggesting that complement activation-related pseudoallergy (CARPA) was not involved in this animal model. Overall, the no observable effect levels in rats and primates were 5- and 15-fold higher than the maximal recommended clinical dose.

3.2 Clinical

The safety pharmacology and toxicology assessments in rats and primates indicated that DEFINITY[®] was likely to be well tolerated in man. Overall evaluation of safety data from 3985 patients in 48 studies (26 in echocardiography and 12 in radiology) supports this conclusion. Based on detailed safety analysis from the 40 studies submitted in the European Marketing Authorization Application, a total of 26% patients had at least 1 new-onset adverse reaction and 7.6% of them were judged to be treatment-related adverse events (AEs). The most common drug-related AEs (reported >1%) were fatigue, headache, dyspnoea, back pain, nausea, flushing, and dizziness. Less commonly reported AEs (0.5%~1.0%) were dysgeusia, chest discomfort, pain NOS, altered sensation, and pain at the injection site.

Several of the clinical studies involved stress testing, which is known to be associated with AEs. Furthermore, no dose relationship was identified for any individual new-onset AE reported for DEFINITY®-treated patients, regardless of mode of administration.

In placebo-controlled studies, a total of 126 (56%) of 224 placebo patients experienced a new-onset AE, while 259 (48%) of 543 patients receiving DEFINITY® experienced a new-onset AE. The profiles of the AEs in the 2 groups were also similar. Adverse event rates in rest-stress echocardiographic imaging studies were higher (56%) than in rest-only studies (24%), attributable mainly to the use of stress agents and additional dosing of the stress patients.

The rates of SAEs and fatal outcomes were low. A total of 34 SAEs were reported from 3985 patients. Out of 34 SAEs, 8 events had fatal outcomes and the remaining 26 SAEs were non-fatal AEs that were classified as serious. None of the SAEs was considered by the investigators to be related to the use of DEFINITY®. No fatal outcome occurred in placebo patients. All of these fatal outcomes occurred at least 1 day after the administration of DEFINITY® and were considered to be not related to drug.

Studies involving specific disease populations were also performed. A clinical study of 38 patients on mechanical ventilation reported no clinically significant abnormalities in any of ventilation safety parameters. These findings are consistent with preclinical studies. A small pharmacokinetic study was performed in chronic obstructive pulmonary disease (COPD) patients with a high (50- μ L/kg) dose of DEFINITY®. No SAEs were observed and the lung clearance of PFP in the COPD patients was similar to the normal controls. Some AEs were reported for both the COPD (7/12) and normal (4/12) patients. In addition, based on review of case report forms from patients with a history of COPD who received at least 1 dose of DEFINITY® in other trials, a total of 10 (22%) of the 46 patients reported at least 1 new-onset of AE. It appears the nature of these events was similar and overall suggests pulmonary compromise did not change DEFINITY®'s effects. Interestingly, no clinically important changes were noted in most of the immunology parameters that were evaluated (CH50; immunoglobulins A, E, G, and M; histamine; anti-double stranded DNA antibody; and tryptase), with the exception of a transient elevation of C3a. Since the increase in C3a levels with this high DEFINITY® dose was not associated with the release of bioactive mediators, there does not appear to have been mast cell or basophile activation or any anaphylactoid / anaphylactic reactions. The fact that DEFINITY® was well tolerated in this limited evaluation of patients with COPD is consistent with the lack of change seen in cardiopulmonary parameters in the preclinical pulmonary-compromised dog studies.

In placebo-controlled studies of patients with CHF, the overall incidence of new-onset AEs appeared to be slightly higher in DEFINITY®-treated patients than in placebo patients (35% vs. 23%). In a study of patients with acute MI, the rate of new-onset AEs was lower than

what was observed for DEFINITY[®]-treated patients in all echocardiography studies (14% vs. 30.5%).

Retrospective analysis of ECG monitoring data for ventricular and atrial premature beats indicates that use of DEFINITY[®] appears not to pose a risk related to development of premature beats because DEFINITY[®] is commonly used with a low-mechanical index mode in clinical practice. (The maximum recommended mechanical index for ultrasound used with DEFINITY[®] is 0.8.)

Based on the above data from all clinical trials, DEFINITY[®] is safe and well tolerated in general in echocardiography and radiology clinical trials and also in the high-risk population of patients with pre-existing cardiac conditions.

In summary, the overall rate of treatment-related AEs in clinical trials was low, based on 3985 patients who received at least 1 dose of DEFINITY[®] in clinical trials. The most frequent treatment-related AEs with DEFINITY[®] were fatigue, headache, dyspnoea, back pain, nausea, flushing, and dizziness. The events were mild-to-moderate in intensity, of short duration, and did not require therapeutic intervention. Therefore, the use of DEFINITY[®] provides a significant diagnostic benefit compared to a small and clinically insignificant risk.

4 POST-MARKETING COMMITMENTS FULFILLED SINCE PREVIOUS ADVISORY COMMITTEE

Three Phase 4 clinical studies that examined the safety of DEFINITY[®] are germane to this discussion of safety – a multicenter safety registry study of routine clinical practice (DMP 115-415, [Section 4.1.1](#)), a study of patients with elevated pulmonary artery systolic pressure (PASP) (DMP 115-416, [Section 4.1.2](#)), and a retrospective database study in critically ill patients (DMP 115-418, [Section 4.1.3](#)). Demographic and baseline characteristics of patients enrolled in these studies, dosing information, and information on AEs are described below and summarized in [Section 4.1.4](#).

In addition, a DMC was created at the Agency's request. The DMC has the responsibility of periodically evaluating accumulated safety data collected at regular intervals and rendering an expert opinion as to whether there has been a change in the existing safety profile of DEFINITY[®], including a change in the nature or frequency of events, or whether a particular population is experiencing an increase in events. A summary of the DMC's meetings and findings is provided in [Section 6.4](#).

4.1 Clinical Studies

4.1.1 DMP 115-415 Safety Registry in Routine Clinical Practice

Patients who enrolled in this multicenter US safety registry were adults who, in the investigator's opinion, required DEFINITY® contrast echocardiography because of suboptimal unenhanced images, were able to participate in the study and its follow-up, could communicate effectively with the staff, and provided informed consent. Pregnant females, patients with a known hypersensitivity to perflutren, patients who had had a prior SAE associated with perflutren or another echocardiography imaging contrast agent, and patients with any condition that might create an undue hazard or prevent effective participation were excluded.

4.1.1.1 Demographic and Baseline Characteristics in DMP 115-415 Safety Registry in Routine Clinical Practice

Demographic and baseline characteristic data from the 1053 patients who completed the study are summarized in [Table 4-1](#). Patients were categorized by the setting in which they received DEFINITY® - rest only, stress only, or rest and stress. Of the 1053 patients, 444 (42.2%) were at least 65 years old. The mean age (standard deviation [SD]) of the study patients was 61.3 (12.9) years. The majority of patients were male (62.0%), White (81.5%), and obese (total mean body mass index [BMI] of 33.5 kg/m²), though there were considerable numbers of Black/African American patients (between 12% and 16%). There were substantial numbers of patients with a BMI of 60 and above in the study, primarily in rest-only and rest-and-stress patient groups. In summary, demographic characteristics were similar across all patient groups.

Table 4-1 Demographic and Baseline Characteristics of Patients in the Safety Registry Study who Received DEFINITY® in Routine Clinical Practice (DMP 115-415)

Characteristic/ Analysis Group	Statistic/Outcome	Rest Only (N = 599)	Stress Only (N = 32)	Rest and Stress (N = 422)	Total (N = 1053)
Age (years)	N	599	32	422	1053
	Mean (SD)	62.7 (13.2)	61.7 (12.4)	59.3 (12.2)	61.3 (12.9)
	Median (min – max)	63 (21 – 97)	63(38 - 85)	60 (25 - 89)	62 (21 - 97)
Age group	N	599	32	422	1053
	< 65 years	318 (53.1%)	18 (56.3%)	273 (64.7%)	609 (57.8%)
	≥ 65 years	281 (46.9%)	14 (43.8%)	149 (35.3%)	444 (42.2%)
Gender	N	599	32	422	1053
	Male	390 (65.1%)	19 (59.4%)	244 (57.8%)	653 (62.0%)
	Female	209 (34.9%)	13 (40.6%)	178 (42.2%)	400 (38.0%)
Ethnicity	N	596	32	413	1041
	Hispanic or Latino	34 (5.7%)	6 (18.8%)	33 (7.8%)	73 (6.9%)
	Not Hispanic or Latino	562 (93.8%)	26 (81.3%)	380 (90.0%)	968 (91.9%)
Race	N	596	32	419	1047
	White	493 (82.3%)	25 (78.1%)	340 (80.6%)	858 (81.5%)
	Asian	2 (0.3%)	2 (6.3%)	9 (2.1%)	13 (1.2%)
	Black/African American	95 (15.9%)	5 (15.6%)	51 (12.1%)	151 (14.3%)
	American Indian/Alaskan Native	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.3%)
	Other	6 (1.0%)	0 (0.0%)	16 (3.8%)	22 (2.1%)
BMI (kg/m ²)	N	599	32	421	1052
	Mean (SD)	33.5 (9.2)	31.5 (8.8)	33.7 (7.9)	33.5 (8.7)
	Median (min - max)	32.0 (15.0 - 85.0)	29.5 (18.0 - 52.0)	33.0 (18.0 - 76.0)	32.0 (15.0 - 85.0)

Note: The denominator for all percentages is the number of nonmissing values.

Cardiac medical history data for the 1053 patients in the safety population are summarized in [Table 4-2](#). The majority of patients had a history of cardiac events or conditions. In total, 65.3% of patients had a history of hypertension, 20.7% had a history of MI, 30.9% had undergone a previous percutaneous coronary intervention (PCI) or coronary artery by-pass graft (CABG), 19.8% had a history of cardiomyopathy, 21.3% had CHF, and 10.3% had acute coronary syndrome. In addition, 80.1% of patients were reported as having “other” cardiac conditions.

Pulmonary medical history is summarized in [Table 4-3](#). A total of 10.1% of patients had a history of COPD and 9.7% had asthma. A total of 23.1% of patients had a history of “other” pulmonary conditions.

Table 4-2 Cardiac Medical History of Patients in the Safety Registry Study who Received DEFINITY® in Routine Clinical Practice (DMP 115-415) (N [%])

Cardiac Medical History	Rest Only (N=599)	Stress Only		Rest and Stress		Total (N=1053)
		Exercise (N=8)	Pharm. (N=24)	Exercise (N=216)	Pharm. (N=206)	
MI	155 (25.9%)	1 (12.5%)	1 (4.2%)	23 (10.6%)	38 (18.4%)	218 (20.7%)
PCI/ CABG	229 (38.2%)	2 (25.0%)	3 (12.5%)	49 (22.7%)	42 (20.4%)	325 (30.9%)
Cardiomyopathy	189 (31.6%)	0 (0.0%)	2 (8.3%)	7 (3.2%)	10 (4.9%)	208 (19.8%)
CHF	193 (32.2%)	0 (0.0%)	2 (8.3%)	6 (2.8%)	23 (11.2%)	224 (21.3%)
Right-left, bi-directional or transient right-left cardiac shunts	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Worsening or clinically unstable CHF	23 (3.8%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	6 (2.9%)	30 (2.8%)
Acute coronary syndrome	61 (10.2%)	2 (25.0%)	3 (12.5%)	22 (10.2%)	20 (9.7%)	108 (10.3%)
Serious ventricular arrhythmia or high risk for arrhythmia due to QT interval prolongation	31 (5.2%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	2 (1.0%)	35 (3.3%)
Hypertension	413 (68.9%)	2 (25.0%)	17 (70.8%)	120 (55.6%)	136 (66.0%)	688 (65.3%)
Other cardiac conditions	503 (84.0%)	5 (62.5%)	15 (62.5%)	171 (79.2%)	149 (72.3%)	843 (80.1%)

Pharm. = Underwent stress with a pharmacological stress agent.

Note: Number and percentage in each category includes patients with a current or previous medical history.

Table 4-3 Pulmonary Medical History of Patients in the Safety Registry Study who Received DEFINITY® in Routine Clinical Practice (DMP 115-415) (N [%])

Pulmonary Medical History	Rest Only (N=599)	Stress Only		Rest and Stress		Total (N=1053)
		Exercise (N=8)	Pharm. (N=24)	Exercise (N=216)	Pharm. (N=206)	
Respiratory failure (CO retention, hypoxemia)	7 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	8 (0.8%)
Severe emphysema, pulmonary emboli, or other comorbidity causing pulmonary hypertension	28 (4.7%)	0 (0.0%)	1 (4.2%)	2 (0.9%)	3 (1.5%)	34 (3.2%)
COPD	64 (10.7%)	0 (0.0%)	4 (16.7%)	8 (3.7%)	30 (14.6%)	106 (10.1%)
Asthma	57 (9.5%)	0 (0.0%)	1 (4.2%)	18 (8.3%)	26 (12.6%)	102 (9.7%)
Mechanical ventilation	12 (2.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	4 (1.9%)	18 (1.7%)
Pulmonary hypertension	12 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	13 (1.2%)
Other pulmonary conditions	170 (28.4%)	0 (0.0%)	1 (4.2%)	42 (19.4%)	30 (14.6%)	243 (23.1%)

Pharm. = Underwent stress with a pharmacological stress agent.

Note: Number and percentage in each category includes patients with a current or previous medical history.

4.1.1.2 Patient Exposure to DEFINITY® in DMP 115-415 Safety Registry in Routine Clinical Practice

Whether expressed as the volume administered or as the volume per unit weight ($\mu\text{L}/\text{kg}$), the overwhelming majority of patients who received DEFINITY® in the safety registry in routine clinical practice were administered a dose that was consistent with the label. Depending on how the dose is expressed, 76% of patients received <1.3 mL DEFINITY® and 68% received < 10 $\mu\text{L}/\text{kg}$, the lowest recommended dose level. Another 23% of patients received 1.3 to 2.6 mL and 26% of patients received 10 to 20 $\mu\text{L}/\text{kg}$. Only a small minority of patients in routine clinical practice received more than the labeled dose.

4.1.1.3 Safety Data From DMP 115-415 Safety Registry in Routine Clinical Practice

Treatment-emergent AEs, including SAEs, were collected from dosing through 24 hours postdose. No deaths or SAEs were reported during this study. Events reported in at least 0.5% of any patient group are presented in [Table 4-4](#). The following AEs were reported in at least 0.5% of all patients: headache (1.2%); nausea (0.9%); back pain (0.7%); tremor (0.6%); and angina pectoris, chest pain, palpitations, ventricular extrasystoles, dizziness, and flushing (each 0.5%). The distribution of certain AEs across the patient groups (eg, angina pectoris and chest pain) suggests that there could be a relationship to stress testing. However, the overall distribution of events is consistent with DEFINITY®'s known safety profile and labeling.

Data were also collected on changes in patients' vital signs. No trends or clinically significant changes were noted for any of the vital sign results for blood pressure, oral temperature, heart rate, respiratory rate, or oxygen saturation.

Table 4-4 Treatment-Emergent Adverse Events (≥ 0.5%) in Patients in the Safety Registry Study who Received DEFINITY® in Routine Clinical Practice (DMP 115-415) (N [%])

Primary System/Organ Class ^a Preferred Term ^a	Rest Only (N = 599)	Stress Only (N = 32)	Rest and Stress (N = 422)	Total (N = 1053)
Patients with at least 1 adverse event	27 (4.5%)	2 (6.3%)	85 (20.1%)	114 (10.8%)
CARDIAC DISORDERS	4 (0.7%)	1 (3.1%)	33 (7.8%)	38 (3.6%)
Angina pectoris	0 (0.0%)	0 (0.0%)	5 (1.2%)	5 (0.5%)
Chest discomfort	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.2%)
Chest pain	0 (0.0%)	0 (0.0%)	5 (1.2%)	5 (0.5%)
Dyspnoea	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.2%)
Dyspnoea exertional	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.2%)
Palpitations	0 (0.0%)	0 (0.0%)	5 (1.2%)	5 (0.5%)
Supraventricular tachycardia	0 (0.0%)	1 (3.1%)	1 (0.2%)	2 (0.2%)
Ventricular extrasystoles	1 (0.2%)	0 (0.0%)	4 (0.9%)	5 (0.5%)
GASTROINTESTINAL DISORDERS	4 (0.7%)	0 (0.0%)	12 (2.8%)	16 (1.5%)
Dry mouth	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.2%)
Nausea	2 (0.3%)	0 (0.0%)	7 (1.7%)	9 (0.9%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (0.7%)	0 (0.0%)	6 (1.4%)	10 (0.9%)
Chest pain	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.2%)
INVESTIGATIONS	4 (0.7%)	0 (0.0%)	5 (1.2%)	9 (0.9%)
Electrocardiogram ST segment depression	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.2%)
Electrocardiogram ST-T change	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (0.8%)	0 (0.0%)	12 (2.8%)	17 (1.6%)
Back pain	1 (0.2%)	0 (0.0%)	6 (1.4%)	7 (0.7%)

Primary System/Organ Class^a Preferred Term^a	Rest Only (N = 599)	Stress Only (N = 32)	Rest and Stress (N = 422)	Total (N = 1053)
NERVOUS SYSTEM DISORDERS	4 (0.7%)	0 (0.0%)	24 (5.7%)	28 (2.7%)
Dizziness	0 (0.0%)	0 (0.0%)	5 (1.2%)	5 (0.5%)
Headache	4 (0.7%)	0 (0.0%)	9 (2.1%)	13 (1.2%)
Paraesthesia	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.2%)
Tremor	0 (0.0%)	0 (0.0%)	6 (1.4%)	6 (0.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.3%)	0 (0.0%)	8 (1.9%)	10 (0.9%)
Dyspnoea	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.3%)
Non-cardiac chest pain	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.3%)
VASCULAR DISORDERS	4 (0.7%)	1 (3.1%)	10 (2.4%)	15 (1.4%)
Flushing	2 (0.3%)	0 (0.0%)	3 (0.7%)	5 (0.5%)
Hypertension	0 (0.0%)	1 (3.1%)	2 (0.5%)	3 (0.3%)
Hypotension	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.3%)

^a Body/organ system and preferred term were coded using the Medical Dictionary for Regulatory Activities (MedDRA Dictionary), Version 11.

4.1.1.4 Summary of DMP 115-415 Safety Registry in Routine Clinical Practice

This FDA Post-Approval Commitment Study examined the safety of DEFINITY® in routine clinical practice in settings of rest only, stress only, and rest and stress. In a population of 1053 patients, 42.2% of whom were at least 65 years old and a majority of whom were obese (mean BMI = 33.5 kg/m²), no SAEs or deaths were recorded. While 10.8% of patients experienced at least 1 AE, only 3.5% of patients experienced an event that was considered treatment-related. Adverse events that were reported in at least 0.5% of all patients included headache (1.2%); nausea (0.9%); back pain (0.7%); tremor (0.6%); and angina pectoris, chest pain, palpitations, ventricular extrasystoles, dizziness, and flushing (each 0.5%). This distribution of events is consistent with DEFINITY®'s known safety profile and labeling.

4.1.2 DMP 115-416 in Patients With Elevated Pulmonary Artery Systolic Pressure

This Phase 4 prospective, open-label, multicenter, nonrandomized controlled clinical trial was conducted as an FDA Post-Approval Commitment Study in which the safety of DEFINITY® was evaluated during rest echocardiography in patients with elevated and normal PASP who were undergoing right-heart catheterization. The primary objective of this study was to evaluate the effect of DEFINITY® on pulmonary artery hemodynamics. The secondary objective was to assess the safety and potential immunologic effects of DEFINITY® administration during right-heart catheterization. Patients with elevated PASP (> 35 and ≤ 75 mmHg) were compared to patients with normal PASP (≤ 35 mmHg).

A total of 34 patients were enrolled in this study. Of those enrolled, 32 patients were eligible to receive DEFINITY®, received 1 dose of DEFINITY®, and completed the study. Two of the patients who were enrolled in this study were withdrawn by the investigator after the catheterization procedure and before receiving DEFINITY®. One of these patients (011-005) required an urgent intervention, and the other patient (011-008) met the exclusion criterion of a baseline PASP of > 75 mmHg, with a baseline PASP measurement of 79 mmHg. Patients with medical conditions or other circumstances that, in the investigator's opinion, would significantly decrease the chances that a patient can complete the study procedures or follow-up evaluations, and patients with severe pulmonary hypertension (ie, PASP > 75 mmHg) were excluded from this study.

4.1.2.1 Demographic and Baseline Characteristics in DMP 115-416 Patients With Normal or Elevated Pulmonary Artery Systolic Pressure

Of the 32 patients who completed the study, 16 patients had elevated PASP defined here as > 35 mmHg at baseline, and 16 patients had normal PASP (≤ 35 mmHg) at baseline. The mean age (SD) of study patients was 57.2 (12.9) years (Table 4-5). The majority of patients

were female (53.1%), not Hispanic or Latino (81.3%), and White (65.6%). Half of the patients enrolled were obese (total mean BMI value [SD] was 31.2 kg/m² [8.8]). The demographic characteristics of age, ethnicity, and race were similar in the 2 groups. The majority of patients in the elevated PASP group were male (56.3%), while the majority of patients in the normal PASP group were female (62.5%). The mean BMI value (SD) was 28.9 kg/m² (8.7) for patients in the elevated PASP group and 33.5 kg/m² (8.5) for patients in the normal PASP group, and the difference in mean BMI values between the elevated and normal PASP patient groups was not statistically significant in this small study population ($p = .068$).

Table 4-5 Demographic and Baseline Characteristics in DMP 115-416 Patients With Normal or Elevated Pulmonary Artery Systolic Pressure

Characteristic/Analysis Group Statistic/Outcome	Elevated PASP (N = 16)	Normal PASP (N = 16)	Total (N = 32)	<i>p</i> -Value ^a
Age (years)				
Mean (SD)	57.4 (15.1)	56.9 (10.8)	57.2 (12.9)	.955
Median	55	58	56	
Minimum - maximum	25 - 82	42 - 77	25 - 82	
Gender				
Male	9 (56.3%)	6 (37.5%)	15 (46.9%)	.479
Female	7 (43.8%)	10 (62.5%)	17 (53.1%)	
Ethnicity				
Hispanic or Latino	1 (6.3%)	5 (31.3%)	6 (18.8%)	.172
Not Hispanic or Latino	15 (93.8%)	11 (68.8%)	26 (81.3%)	
Race				
White	10 (62.5%)	11 (68.8%)	21 (65.6%)	.041
Black or African American	4 (25.0%)	0 (0.0%)	4 (12.5%)	
Native Hawaiian or Other Pacific Islander	1 (6.3%)	0 (0.0%)	1 (3.1%)	
BMI (kg/m ²)				
Mean (SD)	28.9 (8.7)	33.5 (8.5)	31.2 (8.8)	.068
Median	25.9	30.5	30.0	
Minimum - maximum	18.8 - 48.0	18.7 - 56.6	18.7 - 56.6	

^a The *p*-values were calculated from Wilcoxon rank sum test for comparisons of age, height, weight, and BMI between the 2 PASP groups. Fisher's exact test was used for comparisons of gender, ethnicity, and race.

The cardiac history data of the 32 patients in the safety population is summarized in [Table 4-6](#). The majority of patients who received DEFINITY® in this study had a history of

cardiac events or conditions. None of the differences between elevated and normal PASP groups were statistically significant. A total of 71.9% had CHF, 43.8% had a history of cardiomyopathy, 25.0% had undergone a PCI or CABG, 21.9% had a history of MI, 6.3% had serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval, and 3.1% had acute coronary syndrome.

Table 4-6 Cardiac Medical History of Patients Enrolled in the Study of Elevated Pulmonary Artery Systolic Pressure (DMP 115-416) (N [%])

Medical History	Elevated PASP (N = 16)	Normal PASP (N = 16)	Total (N = 32)	p-Value ^a
MI	5 (31.3%)	2 (12.5%)	7 (21.9%)	.394
PCI(s) or CABG(s)	6 (37.5%)	2 (12.5%)	8 (25.0%)	.220
Cardiomyopathy	7 (43.8%)	7 (43.8%)	14 (43.8%)	1.000
CHF	13 (81.3%)	10 (62.5%)	23 (71.9%)	.433
Worsening of clinically unstable CHF	0 (0.0%)	1 (6.3%)	1 (3.1%)	1.000
Acute coronary syndrome	0 (0.0%)	1 (6.3%)	1 (3.1%)	1.000
Serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval	0 (0.0%)	2 (12.5%)	2 (6.3%)	.484
Other cardiac conditions	4 (25.0%)	9 (56.3%)	13 (40.6%)	.149

Note: Numbers and percentages include patients who reported history as either current or previous.

^a The p-values were calculated from Fisher's exact test.

4.1.2.2 Patient Exposure to DEFINITY® in DMP 115-416 Patients With Normal or Elevated Pulmonary Artery Systolic Pressure

Patients received an IV bolus injection of DEFINITY® on Day 1 following right-heart catheterization in accordance with the recommendations for bolus administration described in the US Package Insert.²⁰ The 32 patients who completed this study received a mean dose (SD) of 1.0 mL (0.29) of DEFINITY®, with a range of 0.5 – 1.5 mL. The amount of DEFINITY® administered per patient was calculated based upon patient body weight.

4.1.2.3 Pulmonary Artery Hemodynamic Data From DMP 115-416 in Patients With Normal or Elevated Pulmonary Artery Systolic Pressure

Pulmonary artery hemodynamic assessments were evaluated at baseline and to 33 ± 2 minutes after DEFINITY® administration. DEFINITY® administration did not result in any clinically or statistically significant differences in change from baseline values in systemic hemodynamic assessments (ie, systolic blood pressure, diastolic blood pressure, and

mean blood pressure). Analyses of pulmonary artery hemodynamic measurements reveal no clinically significant changes from baseline and no statistically significant or clinically important differences between patients with elevated PASP and patients with normal PASP (Table 4-7). There was a wide range from minimum to maximum systolic and diastolic blood pressures in these patients. However, these differences did not translate into clinically significant changes in PASP, pulmonary artery diastolic pressure (PADP), mean PAP, right arterial pressure (RAP), cardiac output (CO), or pulmonary capillary wedge pressure (PCWP). Within the elevated and normal PASP patient groups, there was no statistically significant change from baseline, as judged by 95% confidence intervals (CIs). Thus, DEFINITY[®] administration did not have a (statistically) significant effect at postdose timepoints in either patient group. Furthermore, when the difference in the percent change from baseline for each timepoint was compared to zero using a Wilcoxon rank sum test, none was statistically significant (Table 4-7).

Table 4-7 Analyses of Change From Baseline of Hemodynamic Measurements in Patients Enrolled in the Study of Elevated Pulmonary Artery Systolic Pressure (DMP 115-416)

Hemodynamic Parameter Timepoint	Elevated PASP	Normal PASP	Difference (Elevated – Normal)
	% Change from Baseline	% Change from Baseline	<i>p</i> -Value ^a
PASP			
Dose Administration	0.0 (7.92)	-1.1 (16.78)	.890
3 min postdose	-0.9 (8.53)	-0.3 (15.78)	.664
8 min postdose	-1.0 (10.14)	0.3 (11.43)	.724
13 min postdose	-3.2 (9.32)	1.6 (9.50)	.179
18 min postdose	-3.6 (9.55)	2.6 (15.17)	.509
23 min postdose	-0.8 (9.63)	1.0 (17.54)	.648
28 min postdose	-2.8 (10.42)	2.0 (20.08)	.610
33 min postdose	-1.7 (10.25)	-1.9 (18.03)	.242
PADP			
Dose Administration	4.6 (19.85)	-3.0 (22.68)	.196
3 min postdose	10.7 (23.12)	4.3 (28.03)	.274
8 min postdose	4.9 (18.02)	13.6 (43.61)	.372
13 min postdose	4.8 (24.27)	8.7 (32.54)	.592
18 min postdose	10.5 (27.58)	12.0 (32.70)	.850
23 min postdose	3.2 (20.10)	2.1 (39.24)	.635
28 min postdose	4.1 (22.28)	8.7 (42.01)	.836
33 min postdose	13.1 (27.78)	11.2 (53.68)	.250
Mean PAP			
Dose Administration	-4.2 (9.50)	-3.0 (16.83)	.450
3 min postdose	1.0 (10.06)	-1.5 (13.69)	.690
8 min postdose	-0.3 (11.40)	0.9 (13.15)	.803
13 min postdose	-0.4 (10.36)	0.0 (11.18)	.890
18 min postdose	-1.0 (9.88)	-0.8 (21.60)	.940
23 min postdose	-0.5 (11.05)	-1.6 (14.96)	.591
28 min postdose	-0.3 (10.59)	0.3 (15.26)	.955
33 min postdose	-0.1 (15.35)	-0.6 (15.49)	.865

Hemodynamic Parameter Timepoint	Elevated PASP	Normal PASP	Difference (Elevated – Normal)
	% Change from Baseline	% Change from Baseline	<i>p</i> -Value ^a
RAP			
Dose Administration	10.8 (9.29)	9.5 (18.62)	.545
3 min postdose	4.9 (10.36)	1.9 (13.16)	.482
8 min postdose	0.9 (13.05)	1.7 (16.45)	.820
13 min postdose	4.9 (17.18)	9.1 (19.90)	.471
18 min postdose	6.9 (17.51)	2.8 (17.65)	.449
23 min postdose	8.5 (22.01)	-0.6 (26.63)	.309
28 min postdose	2.6 (20.28)	4.9 (23.02)	.895
33 min postdose	6.9 (25.64)	-0.0 (18.46)	.910
CO			
3 min postdose	3.6 (13.75)	4.8 (53.14)	.299
33 min postdose	4.4 (11.23)	7.7 (51.43)	.220
PCWP			
3 min postdose	-4.2 (20.71)	12.6 (25.25)	.162
33 min postdose	1.6 (31.08)	11.2 (30.53)	.374

^a *p*-value from Wilcoxon rank sum test assessed if the difference between the change from Baseline in the elevated and normal PASP patient groups were different from zero.

4.1.1.2.4 Adverse Event Data From DMP 115-416 in Patients With Normal or Elevated Pulmonary Artery Systolic Pressure

A total of 32 of the 34 patients enrolled received 1 dose of DEFINITY®, completed the study, and were included in the safety population for this study. No deaths or SAEs were reported and no patients were discontinued from the study as a result of an AE. In addition, no major hemodynamic changes were reported.

The number of total patients in this study with at least 1 AE was 9 (28.1%), with 5 (31.3%) and 4 (25.0%) patients in the elevated and normal PASP groups, respectively (Table 4-8). The difference in the number of patients with at least 1 AE for patients in the elevated versus normal PASP group was not statistically significant ($p = 1.000$). Given the sample size of 32 patients, every AE that was recorded reached a rate of $\geq 0.5\%$, which was defined as common, as in the US Package Insert.²⁰ For all patients, the AEs were myalgia (15.6%), back pain (6.3%), neck pain (3.1%), chest pain (3.1%), dizziness (3.1%), and headache (3.1%). The rates of occurrence of myalgia (18.8% and 12.5%) and back pain (6.3% and 6.3%) were similar in the elevated and normal PASP patient groups, respectively. Neck pain

and chest pain (6.3%, each) occurred only in patients in the elevated PASP group, whereas dizziness and headache (6.3%, each) occurred only in patients in the normal PASP group.

Table 4-8 Adverse Events Reported in Patients with Normal and Elevated Pulmonary Artery Systolic Pressure (DMP 115-416)

Primary System/Organ Class ^a Preferred Term ^a	Elevated PASP (N = 16)	Normal PASP (N = 16)	Total (N = 32)	p-Value ^b
Patients with at least 1 AE	5 (31.3%)	4 (25.0%)	9 (28.1%)	1.000
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (6.3%)	0 (0.0%)	1 (3.1%)	
Chest Pain	1 (6.3%)	0 (0.0%)	1 (3.1%)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (31.3%)	3 (18.8%)	8 (25.0%)	
Back Pain	1 (6.3%)	1 (6.3%)	2 (6.3%)	
Myalgia	3 (18.8%)	2 (12.5%)	5 (15.6%)	
Neck Pain	1 (6.3%)	0 (0.0%)	1 (3.1%)	
NERVOUS SYSTEM DISORDERS	0 (0.0%)	2 (12.5%)	2 (6.3%)	
Dizziness	0 (0.0%)	1 (6.3%)	1 (3.1%)	
Headache	0 (0.0%)	1 (6.3%)	1 (3.1%)	

^a Body System and Preferred Term are coded using the MedDRA dictionary, V11.

^b The p-value was calculated from Fisher's exact test.

4.1.2.5 Summary of DMP 115-416 in Patients With Elevated or Normal Pulmonary Artery Systolic Pressure

This FDA Post-Approval Commitment Study examined the safety of DEFINITY® during rest echocardiography in patients who were undergoing right-heart catheterization. At baseline, half of the patients had elevated PASP (> 35 mmHg) and half of the patients had normal PASP (≤ 35 mmHg). In a population of 32 patients with a mean age of 57.2 years and a mean BMI of 31.2 kg/m², no SAEs or deaths were recorded. Given the sample size, every AE that was recorded reached the rate of ≥ 0.5%. For all patients, AEs included myalgia (15.6%), back pain (6.3%), neck pain (3.1%), chest pain (3.1%), dizziness (3.1%), and headache (3.1%). Rates were similar in the elevated and normal PASP patient groups. These events are consistent with DEFINITY®'s known safety profile and labeling.

4.1.3 DMP 115-418 Retrospective Database Study in Critically Ill Patients

This retrospective observational database study (DMP 115-418) was based on discharge data from general, acute-care facilities in Premier's Perspective™ database. Adult patients at

least 18 years-of-age in all types of ICUs with a same-day transthoracic echocardiogram (TTE) and a discharge date between 01 January 2002 and 15 June 2008 were included. The study matched patients using a propensity score algorithm to reduce the potential for imbalance in covariates in patients who underwent DEFINITY® and noncontrast echocardiography. Matching of covariates was performed using a “Greedy Match” algorithm.^{21, 22}

For the primary outcome analysis, baseline demographics and other covariates were compared for imbalances. The following list of covariates/confounding variables was used to adjust the model for imbalance between patient groups:

- Race
- Admission type (emergency, elective, trauma, urgent)
- Admission source (physician referral, transfer from another facility, emergency room)
- Gender
- 3M™ All Payer Refined – Diagnosis Related Group (APR-DRG)
- Severity of illness (minor, moderate, major, extreme)
- Risk of mortality (minor, moderate, major, extreme)
- Discharge status
- Attending physician specialty
- Comorbidities (23), listed in [Table 4-10](#)
- Age (either categorical or continuous)
- Bed size of hospital
- Teaching hospital
- Geographical region (Northeast, South, Midwest, West)
- Population served (urban/rural)

4.1.3.1 Demographic and Baseline Characteristics in DMP 115-418 Retrospective Study in Critically Ill Patients

After employing the matching algorithm, 31,596 patients were further analyzed in the matched dataset (15,798 patients in each of the noncontrast and DEFINITY® groups). [Table 4-9](#) and [Table 4-10](#) present selected demographic characteristics and all 23 comorbidities for the subset of matched patients. A high degree of match was obtained for demographic characteristics and for all clinical comorbidities. After completion of the match, over 90% of the original sample size for the DEFINITY® group was included in the matched dataset. Even for comorbidities with substantial sample size, matching was successful, as there were no statistically significant differences in the frequencies of 23 comorbidities between DEFINITY® and noncontrast patient groups ([Table 4-10](#)).

Table 4-9 Selected Patient Demographic Characteristics in the Matched Dataset of the Retrospective Database Study of Critically Ill Patients (DMP 115-418)

Demographic Characteristic Category	Noncontrast Group N=15,798		DEFINITY® Group N=15,798		p-Value ^a
	Discharges (N)	Percentage (%)	Discharges (N)	Percentage (%)	
Age (years)					
18-44	1,189	7.53%	1,240	7.85%	
45-64	6,142	38.88%	6,064	38.38%	
65-74	4,127	26.12%	4,048	25.62%	
75-79	1,908	12.08%	1,961	12.41%	
80+	2,432	15.39%	2,485	15.73%	.458
Gender					
Male	5,795	36.68%	5,856	37.07%	
Female	10,003	63.32%	9,941	62.93%	
Unknown	0	0.00%	1	0.01%	.470
Race					
White	11,607	73.47%	11,614	73.52%	
Black	1,902	12.04%	1,804	11.42%	
Hispanic	231	1.46%	253	1.60%	
Other	2,058	13.03%	2,127	13.46%	.193

^a A 2-sided multivariate Chi-square test was performed at the 5% level of significance.

Table 4-10 **Frequencies of 23 Comorbid Conditions in Patients in the Matched Dataset of the Retrospective Database Study of Critically Ill Patients (DMP 115-418)**

Comorbid Condition	Noncontrast Group N=15,798		DEFINITY® Group N=15,798		p-Value ^a
	Discharges (N)	Percentage (%)	Discharges (N)	Percentage (%)	
CHF	7,410	46.91%	7,340	46.46%	.430
Ventricular arrhythmias	2,266	14.34%	2,229	14.11%	.551
Hypertension	7,286	46.12%	7,228	45.75%	.513
Renal failure	5,801	36.72%	5,779	36.58%	.797
Venous catheterization for renal dialysis	835	5.29%	854	5.41%	.635
Hemodiafiltration, hemofiltration	1,186	7.51%	1,256	7.95%	.140
Peritoneal dialysis	28	0.18%	32	0.20%	.605
Diabetes	6,530	41.33%	6,455	40.86%	.391
COPD	5,141	32.54%	5,252	33.25%	.184
Pneumonia	3,542	22.42%	3,486	22.07%	.449
Stroke	1,398	8.85%	1,422	9.00%	.636
Sepsis	777	4.92%	846	5.36%	.079
Septic shock	1,135	7.18%	1,153	7.30%	.696
Anaphylactic shock	15	0.10%	13	0.08%	.705
Gastrointestinal hemorrhage	620	3.93%	651	4.12%	.375
Transfusion procedure	3,201	20.26%	3,220	20.38%	.791
MI	5,841	36.97%	5,758	36.45%	.333
Acute coronary syndrome	696	4.41%	712	4.51%	.663
Pulmonary hypertension	1,566	9.91%	1,592	10.08%	.626
Intra-aortic balloon pump	217	1.37%	211	1.34%	.770
Cardiogenic shock	1,134	7.18%	1,052	6.66%	.069
Mechanical ventilation	5,647	35.75%	5,675	35.92%	.703
Continuous positive airway pressure	679	4.30%	749	4.74%	.058

^a For all comparisons, a 2-sided multivariate Chi-square test was performed at the 5% level of significance.

As presented in [Table 4-9](#) and [Table 4-10](#), the Greedy Match propensity analysis resulted in noncontrast and DEFINITY® groups containing very similar patient populations across demographic characteristics and 23 major comorbid conditions. Of note, the DEFINITY® and noncontrast groups were highly matched for acute MI and other unstable coronary

syndromes, CHF, respiratory failure requiring mechanical ventilation, and pulmonary hypertension.

4.1.3.2 Analyses of Mortality in DMP 115-418 Retrospective Study in Critically Ill Patients

A significantly smaller percentage of patients died in the DEFINITY® group than in the noncontrast group during the 48 hours after contrast administration (Table 4-11).

There was a relative reduction of 32% in mortality and an absolute reduction of approximately 1% (3.09% vs. 2.14%) for the DEFINITY® group compared with the noncontrast group. Of note, these differences were observed in a large population of patients and included a substantial number of endpoints of death. Consequently, the differences were highly statistically different.

The number of deaths which occurred in the noncontrast echocardiography group indicates that there is a baseline risk of death from underlying disease processes and thus, in those patients receiving DEFINITY®, the relationship between contrast administration and any serious adverse event is difficult to establish.

Table 4-11 Comparison of 48-Hour Mortality in DMP 115-418 for Critically Ill Patients with Noncontrast or DEFINITY® Echocardiography (Matched Dataset)

Noncontrast Group			DEFINITY® Group			Odds Ratio	
N	# Died	% Died	N	# Died	% Died	Odds ratio ^a	95% CI
15,798	488	3.09%	15,798	338	2.14%	0.683	(0.591, 0.789)

^a Full model logistic regression adjusted odds ratio

Note: Cochran-Mantel Haenszel odds ratio = 0.686 with 95% CI = (0.596, 0.789)

Forty-eight hour mortality rates were also analyzed across different major comorbidities (ie, diagnoses) in critically ill patients and are presented in Table 4-13. The percentage of patients who died in the noncontrast and DEFINITY® groups were compared for each major comorbidity. For 21 of 23 (91.3%) comorbidities, the percentage of patients who died was lower in patients who received DEFINITY®. Of note, patients with acute MI, mechanical ventilation, CHF, cardiogenic shock, and pulmonary hypertension had significantly lower death rates in the DEFINITY® than in the noncontrast group. While multiplicity issues preclude making a definitive causal association between these findings of lower mortality and use of DEFINITY®, the unidirectional trend toward improved survival in patients who received DEFINITY® is highly unlikely to be due to chance.

In addition, all-cause mortality in critically ill patients with mortality reported at any time during their hospital stay was determined for the matched dataset. The results are presented in [Table 4-11](#).

Patients in the DEFINITY® group experienced all-cause mortality at significantly lower rates ($p < .001$) than patients in the noncontrast group. The odds ratio from a full model logistic regression was 0.834 in the matched dataset with an upper bound of the 95% CI that was less than 1.0.

Table 4-12 Comparison of Hospital Stay, All-Cause Mortality in DMP 115-418 for Critically Ill Patients with Noncontrast or DEFINITY® Echocardiography (Matched Dataset)

Noncontrast Group			DEFINITY® Group			Odds Ratio	
N	# Died	% Died	N	# Died	% Died	Odds ratio ^a	95% CI
15,798	2,616	16.56%	15,798	2,321	14.69%	0.834	(0.779, 0.892)

^a Full model logistic regression adjusted odds ratio

Note: Cochran-Mantel Haenszel odds ratio = 0.868 with 95% CI = (0.817, 0.922).

Chi-square test for mortality difference between groups = $p < .001$.

Table 4-13 Comparison of 48-Hour Mortality for Critically Ill Patients with Noncontrast or DEFINITY® Echocardiography by Major Comorbidity (Matched) (DMP 115-418)

Comorbidity	Noncontrast Group			DEFINITY® Group			p-Value ^a
	N	Number Died	Percentage Died	N	Number Died	Percentage Died	
CHF	7,410	196	2.65	7,340	146	1.99	.008
Ventricular arrhythmias	2,266	146	6.44	2,229	110	4.93	.030
Hypertension	7,286	185	2.54	7,228	123	1.70	<.001
Renal failure	5,801	280	4.83	5,779	190	3.29	<.001
Venous catheterization for renal dialysis	835	36	4.31	854	29	3.40	.328
Hemodiafiltration, hemofiltration	1,186	34	2.87	1,256	34	2.71	.810
Peritoneal dialysis	28	0	0.00	32	1	3.13	.533
Diabetes	6,530	191	2.92	6,455	133	2.06	.002
COPD	5,141	140	2.72	5,252	93	1.77	.001
Pneumonia	3,542	103	2.91	3,486	66	1.89	.006
Stroke	1,398	40	2.86	1,422	37	2.60	.673
Sepsis	777	24	3.09	846	29	3.43	.701
Septic shock	1,135	78	6.87	1,153	65	5.64	.223
Anaphylactic shock	15	1	6.67	13	0	0.00	.536
Gastrointestinal hemorrhage	620	32	5.16	651	21	3.23	.085
Transfusion procedure	3,201	99	3.09	3,220	60	1.86	.002
MI	5,841	204	3.49	5,758	135	2.34	<.001
Acute coronary syndrome	696	7	1.01	712	4	0.56	.156
Pulmonary hypertension	1,566	54	3.45	1,592	34	2.14	.025
Intra-aortic balloon pump	217	2	0.92	211	1	0.47	.579
Cardiogenic shock	1,134	106	9.35	1,052	66	6.27	.008
Mechanical ventilation	5,647	336	5.95	5,675	235	4.14	<.001
Continuous positive airway pressure	679	18	2.65	749	17	2.27	.642

^a Chi-square/Fisher's exact test

4.1.3.3 Summary of DMP 115-418 Retrospective Study in Critically Ill Patients

Over 1 million critically ill patients' records were evaluated in this study, which compared the risk of 48-hour and in-hospital mortality in patients undergoing clinically indicated echocardiography with or without DEFINITY[®] contrast enhancement. The Greedy Match algorithm resulted in highly matched noncontrast and DEFINITY[®] groups across all demographic and comorbid conditions, including those patients with pulmonary hypertension.

The propensity matched data demonstrated a relative decrease in the odds ratio of 32% and an absolute reduction of approximately 1% for 48-hour all-cause mortality in the DEFINITY[®] group compared to the noncontrast group. This absolute difference in mortality increased by hospital discharge, such that in-hospital mortality for the DEFINITY[®] group was approximately 2% lower than for the noncontrast group. Thus, the early advantage for patients imaged with DEFINITY[®] was more pronounced by the time of discharge.

Therefore, the available evidence suggests that common disease states in critically ill patients who have echocardiography with DEFINITY[®] are not associated with an increased risk of mortality compared to similar patients who have noncontrast echocardiography. This study did not address the mechanism(s) behind these mortality findings. Large biases in the data are minimized by the propensity matching across common serious illnesses. Other possible explanations for these results include improved patient management after use of DEFINITY[®] and/or the avoidance of other hazardous tests.

4.1.4 Conclusions Based on Clinical Studies

The 3 studies discussed above contribute valuable information to the overall safety profile of DEFINITY[®]. Study DMP 115-415 showed that DEFINITY[®] is well tolerated in the real-world clinical setting. Study DMP 115-416 addressed a concern raised by FDA about the potential adverse effect of DEFINITY[®] on PAP. This study did not find any impact of DEFINITY[®] dosing on AEs in this small, well controlled study. This conclusion is supported by results of a larger clinical study in patients with elevated PASP (≥ 50 mmHg) that found no significant difference in short-term events between contrast and noncontrast cohorts.¹ The authors concluded that right ventricular systolic pressure had no impact on predisposition to adverse outcomes in patients undergoing stress echocardiography in the population studied. Study DMP 115-418 used a large, validated retrospective database to carefully assess the risk associated with DEFINITY[®] use in well matched cohorts of patients who received echocardiography. Although this study was retrospective, the large patient population and propensity matching allow for a comparison that would be highly impractical to address using a prospective clinical trial. This study showed that the use of contrast was associated with a decreased risk of mortality at 48 hours and throughout the hospitalization.

While the mechanism for the decreased mortality was not explored, it is plausible that improved left ventricular opacification and improved diagnostic accuracy may contribute to more clinically targeted treatment. Overall, these studies show a strong and well established safety profile.

5 LITERATURE REVIEW

5.1 Individual Publications

In the interval since 2008, several large single and multicenter studies of microbubble contrast agents have been published in peer-reviewed journals. These studies are summarized in [Table 5-1](#). The studies summarize data from patient populations in which echocardiography is performed at rest or under either exercise or pharmacologic stress testing conditions in routine clinical practice. Many of these studies represent large retrospective, case-control studies from independent investigations.

Two studies included data on DEFINITY[®]-enhanced resting echocardiography among hospitalized patients^{6,23} and a third study investigated consecutively enrolled patients with technically difficult resting echocardiographic studies.³ The final DEFINITY[®]-specific article is a case review and commentary that discusses death rates in the light of pseudo-complications and adverse reactions to other classes of contrast agents.¹⁶ All other studies include pooled data on both DEFINITY[®] and OPTISON[™]. Two studies included patients undergoing either rest or stress echocardiography.^{24,25} Four studies refer to patients undergoing stress echocardiography only,²⁶⁻²⁹ and 1 is a meta-analysis.⁴

Kusnetzky et al reported on the results of a retrospective review of data at a single center in which they examined short-term mortality following either noncontrast or DEFINITY[®]-enhanced echocardiography exams.²³ As shown in [Table 5-1](#), there was no significant difference in overall mortality. However, the acuity of illness and number of comorbid conditions were both greater in the DEFINITY[®] group than in the noncontrast group.

Following this study, Main et al also examined short-term mortality in unselected patients over the period January 2002 through October 2007 (pre-Boxed Warning).⁶ Data were collected from the validated Premier Perspective[™] database. Data were gathered from over 500 hospitals across the Premier network in the USA. Analyses of mortality in groups receiving resting transthoracic echocardiography with or without DEFINITY[®] (as determined by clinical practice needs) again found no difference between groups. Analyses showed that the acuity of illness and baseline pretest risk of mortality due to underlying diseases were greater in the DEFINITY[®] group than in the noncontrast group. Multivariate regression

modeling revealed that the baseline risk-adjusted odds ratio for death was 24% lower in the DEFINITY[®] group than in the noncontrast group.

Kurt et al reported on a prospective study involving 632 consecutively enrolled patients with technically difficult echocardiographic studies who received DEFINITY[®] as part of routine clinical diagnostic care,³ according to the ASE Consensus Statement.⁷ The consecutive DEFINITY[®] contrast studies represented 14.5% of the total echocardiograms performed at the hospital. The authors found that, after DEFINITY[®] echocardiography, the percent of uninterpretable studies decreased from 11.7% to 0.3% and technically difficult studies decreased from 86.7% to 9.8% ($p < 0.0001$). Use of DEFINITY[®] was associated with an increase in the mean number of endocardial wall segments visualized from 11.6 without contrast in the suboptimal baseline studies to 16.8 of 17 segments visualized with DEFINITY[®]. Consequently, new wall motion abnormalities were seen in 28% of DEFINITY[®] studies. In 16.7% of cases, the global left ventricular ejection fraction changed by $\geq 10\%$ with DEFINITY[®] compared with noncontrast echocardiography.

Use of DEFINITY[®] also yielded important findings relative to the detection of left ventricular thrombus by improving left ventricular opacification. In noncontrast baseline studies, left ventricular thrombus was suspected in 35 patients and was assessed as definite in 3 patients. After DEFINITY[®] echocardiography, only 1 of the 35 patients had a suspected thrombus, while 5 additional patients in whom no thrombus had been suspected were identified as having a thrombus ($p < 0.0001$).

The authors also assessed the impact of the echocardiographic results on patient management. The use of DEFINITY[®] led to additional diagnostic tests being avoided in 32.8% of patients, drug management alteration in 10.4% of patients, and an overall change in management in 35.6% of patients. The effect of contrast increased with worsening quality of the unenhanced study, especially in ICUs among critically ill patients.

In summary, Kurt et al demonstrated a clear link between improvements in left ventricular opacification and endocardial border delineation and the ability to make diagnoses that differed from those achievable with noncontrast echocardiography. This had a significant impact on patient management decisions, especially in critically ill patients.

5.2 Meta-Analysis Publications

Khawaja et al published an important meta-analysis of adverse cardiovascular events associated with echocardiographic contrast agents.⁴ The authors utilized a number of well recognized databases from inception to October, 2009 to perform a systematic review and meta-analysis with respect to MI and all-cause mortality. A total of 8 publications reported death as an outcome and 4 reported on MI. The incidence of death in the contrast group was

0.34% (726 of 211,162 patients) compared to 0.9% (45,970 of 5,078,666 patients) in the noncontrast group, with a pooled odds ratio of 0.57 (95% confidence interval of 0.32-1.01, $p = 0.05$). The reported incidence of MI in the contrast group was 0.15% (86 of 57,264 patients) compared to 0.2% (92 of 44,503 patients) in the noncontrast group, with a pooled odds ratio of 0.85 (95% CI 0.35 to 2.05, $p = 0.72$). Significant heterogeneity in the patient populations was seen among the studies. However, in sensitivity analyses the results were not sensitive to these population variations. The authors concluded that the cumulative evidence from these studies of contrast agents for echocardiography did not suggest any contrast-related increase in the incidence of MI or mortality. A significant proportion of the patients in these studies received DEFINITY®. The authors did not provide sub-analyses of the different available contrast agents.

Table 5-1 Table of Relevant DEFINITY® Publications

Study	Study Type (eg, cohort or case/control)	Population Studied	Duration (study period)	Number of Persons (in each group or of cases and controls)	Comments or Results
Khawaja, 2010 ⁴	Meta-analysis	Publications included had reported MI and/or all-cause mortality with contrast echocardiography. Publications must have compared AE rates for MI or all-cause mortality.	Searched MEDLINE, EMBASE, BIOSIS, and Cochrane databases from inception to Oct 2009	8 articles met criteria, including 211,162 CE patients and 5,078,666 NCE patients with mortality data from 8 articles. 57,264 CE patients and 44,503 NCE patients with MI data from 4 articles	0.34% of patients died with CE compared to 0.9% with NCE ($p = .05$). 0.15% of patients had MI with CE compared to 0.2% with NCE ($p = .72$).
Abdelmoneim, 2009 ²⁶	Retrospective, cohort	Undergoing stress echocardiography (exercise or pharmacologic stress)	01Nov2003 - 31Dec2007	10,792 CE (DEFINITY® and OPTISON™) 15,982 NCE (no contrast)	CE cohort had older patients, a higher percentage of males, and higher risk patients than the NCE cohort at baseline. No increased mortality or increased MI with CE vs. NCE.
Anantharam, 2009 ²⁷	Retrospective, cohort	Undergoing stress echocardiography (exercise of pharmacologic stress)	Jan 2004 – Jul 2008	Suspected acute coronary syndrome: 461 CE (DEFINITY® and SonoVue®) 468 NCE (no contrast) Stable chest pain: 689 CE (DEFINITY® and SonoVue®) 2,086 NCE (no contrast)	CE cohort had more risk factors than NCE cohort. No deaths were reported. No increased MI with CE vs. NCE.

Study	Study Type (eg, cohort or case/control)	Population Studied	Duration (study period)	Number of Persons (in each group or of cases and controls)	Comments or Results
Dolan, 2009 ²⁴	Retrospective, cohort	Undergoing echocardiography at rest or stress (exercise or pharmacologic stress)	1999 - 2007	Rest echo: 23,659 CE (DEFINITY® and OPTISON™) 5,900 NCE (no contrast) Pharm stress echo: 6,513 CE 6,249 NCE (no contrast) Exercise stress echo: 4,275 CE 9,740 NCE	No increased mortality or increased MI with CE vs. NCE.
Kurt, 2009 ³	Prospective, cohort	Undergoing rest noncontrast echocardiography and had technically difficult studies.	June 2007 – October 2007	632 patients who received DEFINITY® contrast	After use of contrast, uninterpretable studies decreased from 11.7% to 0.3% and technically difficult studies decreased from 86.7% to 9.8% (<i>p</i> < .0001). Significant impacts on patient management were also observed and a cost-benefit analysis found significant saving with use of contrast.

Study	Study Type (eg, cohort or case/control)	Population Studied	Duration (study period)	Number of Persons (in each group or of cases and controls)	Comments or Results
Gabriel, 2008 ²⁸	Retrospective, cohort	Undergoing stress echocardiography (exercise or pharmacologic stress)	1998 - 2007	Pharm stress echo: 2,022 CE (DEFINITY® and OPTISON™) Exercise stress echo: 2,764 CE 5,012 NCE, matched for test year and test type 57 CE with moderate to severe pulmonary hypertension.	No increase in SAEs, deaths, cardiac arrest, or sustained ventricular tachycardia. No SAEs in CE patients with moderate or severe pulmonary hypertension.
Kusnetzky, 2008 ²³	Retrospective, cohort	Hospitalized; undergoing echocardiography	Jan 2005 - Oct 2007	6,196 CE (DEFINITY®) 12,475 NCE (no contrast)	0.4% of patients died within 24 hrs of echo; no increased mortality in CE vs. NCE
Main, 2008 ⁶	Retrospective, cohort	Hospitalized; undergoing echocardiography	01Jan2002 - 31Oct2007	Full dataset contains > 4.3 MM patients 58,254 CE (DEFINITY®) 4,242,712 NCE (no contrast)	CE patients 24% less likely to die with 1 day compared to NCE

Study	Study Type (eg, cohort or case/control)	Population Studied	Duration (study period)	Number of Persons (in each group or of cases and controls)	Comments or Results
Shaikh, 2008 ²⁹	Retrospective, cohort	Undergoing stress echocardiography (exercise or pharmacologic stress)	21Dec1999 – 09Nov2007	2,914 CE (DEFINITY® and OPTISON™) 2,155 NCE (no contrast)	CE cohort was older and had more risk factors than NCE cohort. No increased ventricular tachycardia, ventricular fibrillation, cardiac arrest, death, acute MI, anaphylactoid reaction, or clinically significant arrhythmias with CE vs. NCE.
Wei, 2008 ²⁵	Retrospective, cohort	Undergoing echocardiography at rest or stress (exercise or pharmacologic stress)	01Jan2001 – 30Sep2007	78,383 CE (DEFINITY® and OPTISON™), including 66,164 DEFINITY® 780,243 NCE (no contrast)	CE cohort had higher % of females and had larger BMI than NCE cohort. 0.01% of patients had SAEs reported as probably related to DEFINITY®, including 4 (0.006%) compatible with being severe anaphylactoid or CARPA reactions. No deaths reported.

Study	Study Type (eg, cohort or case/control)	Population Studied	Duration (study period)	Number of Persons (in each group or of cases and controls)	Comments or Results
Main, 2007 ¹⁶	Opinion piece, case review	Post-marketing deaths following DEFINITY® administration	Not applicable	Review of the 4 patients. Risk of death was calculated.	If all deaths were attributed to DEFINITY®, the mortality rate (1:500,000) is lower than for diagnostic coronary angiography (1:1,000) and the risk of MI or death with exercise treadmill testing (1:2,500). The author also recommended that any future FDA warning address the possible influence of pseudocompli- cation.

CE = contrast echocardiography; NCE = noncontrast echocardiography

5.3 Literature Conclusions

Lantheus concludes that the recently published literature on the safety of DEFINITY®-enhanced echocardiography does not indicate an overall risk of harm compared with noncontrast echocardiography across a broad range of patient care settings and patient populations. Furthermore, there is evidence of significant clinical benefit with use of DEFINITY®. Our conclusions encompass the use of DEFINITY®-enhanced echocardiography for resting and stress echocardiography, including patients with stable and unstable cardiac and pulmonary conditions.

6 SUMMARY OF POST-MARKETING DATA

6.1 Product Distribution

As referenced in [Section 2](#), DEFINITY® was first approved for sale by Health Canada in December 2000 and by the FDA in 2001. It is also currently available in Australia, New Zealand, Mexico, Israel, the UAE, and various countries in Asia. It was recently launched in India. Data available for the time period of 28 December 2007 – 27 December 2010 indicate that approximately 1,083,000 patients, worldwide, received DEFINITY® during that time interval (Source: internal sales data). To date, approximately 2.9 million patients have received product since launch.

Table 6-1 Foreign Marketing of DEFINITY®

Country	Approval Date	Indications	Comment
Canada	12/28/2000	Echocardiography and Radiology	Marketed
US	7/31/2001	Echocardiography	Marketed
Mexico	7/23/2004	Echocardiography and Radiology	Marketed
Israel	7/7/2005	Echocardiography and Radiology	Marketed
Europe	9/20/2006	Echocardiography	Not currently marketed
India	3/11/2010	Echocardiography and Radiology	Marketed
Australia	1/10/2007	Echocardiography and Radiology	Marketed
Korea	1/17/2007	Echocardiography	Marketed
Singapore	6/25/2007	Echocardiography	Marketed
UAE	7/11/2007	Echocardiography	Marketed
New Zealand	12/6/2007	Echocardiography and Radiology	Marketed

6.2 Safety Surveillance Methods and Process: Overview

6.2.1 Summary

Safety surveillance at LMI is an ongoing multidisciplinary function with robust procedures and leadership oversight. Lantheus has instituted proactive and uniquely user-friendly methods of obtaining information on the safety of our products. We include readily identifiable toll-free and local numbers on all product prescribing information, which connects callers directly to our adverse reporting line. Adverse events can also be reported via the DEFINITY® website. Lantheus recognizes that post-marketing surveillance is often limited by under-reporting of adverse outcomes, which is why we have made reporting such events as easy as possible. The PV System consists of the following: collecting, assessing, storing, and reporting of all reports of AEs and SAEs; weekly review of the medical literature

for articles relevant to product safety; quarterly safety signal detection reports; conduct of post-marketing safety studies; operational oversight of a post-marketing DMC; education of health care providers; and reporting of safety to relevant regulatory authorities (eg, FDA, European Medicines Agency [EMA], Health Canada, Therapeutic Goods Administration [TGA]) on a periodic basis, determined by regulatory requirements. Finally, the importance of safety to the LMI organization is underscored by the timely communication and involvement of a senior leadership team (the Medical Safety Review Team [MSRT]), which reviews safety data on at least a quarterly basis. Though we continually seek to improve the robustness of the PV system, we believe that at present its processes and procedures allow us to make an accurate, rapid assessment of the safety profile of our products.

6.2.2 Training/Awareness of Adverse Event Reporting Requirements

All LMI employees are required to train on PV reporting procedures. In particular, Medical Liaison, Sales, and Customer Service personnel are trained shortly after joining the company on the AE reporting procedures, as such staff are most likely to encounter a report of an AE either from on-site or telephone contact with health care providers. In addition, LMI has formal Safety Data Exchange Agreements (SDEAs) with all foreign distributors. The SDEA clearly describes the expectations for AE reporting should a distributor receive information from a customer of health care institution.

6.2.3 Adverse Event Processing

The PV function resides within the Global Medical Affairs department, which is within the Clinical Development and Medical Affairs organization. Pharmacovigilance activities are conducted by LMI from the corporate site in N. Billerica, Massachusetts. Lantheus oversees the global pharmacovigilance (GPV) Agent (i3 Drug Safety), a contract research organization based in Ann Arbor, Michigan.

6.2.4 Medical Literature Review

On a weekly basis, LMI reviews the worldwide literature for any reports that are relevant to product safety. In particular, this search seeks to identify any Individual Case Safety Reports (ICSRs), which need to be reported to relevant regulatory authorities. In addition, the review examines information on other microbubble products to assess any possible class effects relevant to patient safety.

6.2.5 Safety Signal Detection

On a quarterly basis, LMI conducts a formal safety signal detection process for DEFINITY®, which allows us to rapidly determine if any new safety signals have emerged or if the rate of

a known AE has increased compared to historical rates. Any new safety signals are rapidly escalated to the MSRT for consideration and possible action. Examples of the signal detection outputs are discussed in [Section 6.3](#).

6.2.6 Post-Marketing Data Monitoring Committee

Lantheus has an ongoing DMC, which has reviewed AE information since January, 2008. The committee has independently reviewed safety data and has not identified any new safety concerns.

6.2.7 Education of Health Care Providers

Lantheus is also committed to appropriate and timely healthcare provider education regarding important changes to the DEFINITY® label, especially concerning safety issues. The company sponsors educational forums and assures that presentation slides and other print material contain relevant safety information. We provide safety information through product labeling, direct healthcare provider letters describing any labeling changes, web casts associated with major label changes, and medical information through our central medical affairs service and through our US field Medical Affairs Liaisons. All staff who interact with healthcare providers are fully trained on current prescribing information.

6.2.8 Aggregate Safety Reporting

On a periodic basis, as required by relevant regulations, LMI provides formal aggregate summaries of safety data. The two most well known summaries are the Periodic Adverse Drug Event Report (PADER to FDA) and the Periodic Safety Update Report (PSUR to the EMA). These reports provide valuable summaries of events that occurred during the relevant time interval and they identify whether any new safety signals were observed. Lantheus submits these reports in a timely fashion.

6.3 Safety Surveillance: Results

6.3.1 Adverse Events/Reactions

We recognize the uncertainties of AE rates based upon estimates derived primarily from spontaneous reports from physicians in clinical practice. However, reporting rates for DEFINITY® may be higher than for over-the-counter or outpatient therapeutics since DEFINITY® is always administered in an authorized clinical facility such as hospital or outpatient clinics. Patients are attended by sonographers and /or physicians in all cases. It is likely that health care providers are more likely to report events such as anaphylaxis and

death than many other events. While post-marketing data are valuable for safety assessment and are a major aspect of the signal detection process, there are inherent limitations.

Post-marketing presentations of individual events are reported as the number of events (not patients) reported to the i3 safety database during the 3-year interval. This provides the clearest way in which to inform the Advisory Committee of the nature of events that may occur with DEFINITY[®]. The rate at which each preferred term was reported was calculated by dividing the number of events by the total number of vials sold during the same 3-year interval (approximately 1,083,000 vials). The number of vials sold was determined from internal sales figures.

6.3.2 Overall Post-Marketing Experience

The most frequently reported AEs for patients treated with DEFINITY[®] during the post-marketing experience (from 28 December 2007 – 27 December 2010) are presented below, regardless of indication, dose of DEFINITY[®] administered, or mode of administration (bolus injection vs. infusion). While these data provide an overall frequency of AEs reported in patients who received DEFINITY[®], there is no comparator that would allow calculation of the background rates of events in this population.

A total of 1,915 events, representing 998 cases, were received during the post-marketing interval described earlier. All events (preferred terms) were summed and MedDRA System Organ Classes that represent at least 3% of all events were further analyzed. The rates at which events belonging to these System Organ Classes were reported are shown in [Table 6-2](#).

Table 6-2 All Adverse Events Reported During Post-Marketing Experience (28 Dec 2007 – 27 Dec 2010) in Each System Organ Class

System Organ Class	Number (Rate) of Events (Denominator ≈ 1,083,000 vials sold)
Musculoskeletal and connective tissue disorders	682 (0.0630%)
Nervous system disorders	212 (0.0196%)
Skin and subcutaneous tissue disorders	188 (0.0174%)
General disorders and administration site conditions	188 (0.0174%)
Respiratory, thoracic and mediastinal disorders	148 (0.0137%)
Gastrointestinal disorders	112 (0.0103%)
Vascular disorders	98 (0.0090%)
Investigations	74 (0.0068%)
Cardiac disorders	73 (0.0067%)
Immune system disorders	62 (0.0057%)

Out of a total of 1,915 AEs reported, 272 serious events were reported in 169 patients. The most frequently reported preferred terms for SAEs in the System Organ Classes displayed in [Table 6-2](#) are listed in order of descending frequency in [Table 6-3](#). Even the most commonly reported SAEs were reported at rates of less than 1 event per 50,000 vials. The most commonly reported SAE was dyspnoea.

Table 6-3 Serious Adverse Events Reported During the Post-Marketing Experience (28 Dec 2007-27 Dec 2010) by Preferred Term

Preferred Term	Number (Rate) of Events (Denominator ≈ 1,083,000 vials sold)
Dyspnoea	21 (0.00194%)
Hypersensitivity	19 (0.00175%)
Anaphylactic reaction	15 (0.00139%)
Hypotension	11 (0.00102%)
Cardiac arrest	11 (0.00102%)
Ventricular tachycardia	11 (0.00102%)
Chest pain	9 (0.00083%)
Anaphylactoid reaction	7 (0.00065%)
Respiratory distress	7 (0.00065%)
Back pain	7 (0.00065%)
Urticaria	6 (0.00055%)
Myocardial infarction	6 (0.00055%)

Preferred Term	Number (Rate) of Events (Denominator ≈ 1,083,000 vials sold)
Hypertension	5 (0.00046%)
Atrial fibrillation	5 (0.00046%)
Blood pressure decreased	5 (0.00046%)
Loss of consciousness	5 (0.00046%)
Death	5 (0.00046%)
Syncope	5 (0.00046%)
Cardio-respiratory arrest	4 (0.00037%)
Throat tightness	4 (0.00037%)
Hypoxia	4 (0.00037%)
Coma	4 (0.00037%)
Flushing	4 (0.00037%)

A total of 1,643 nonserious events were reported in 903 patients in the post-marketing setting from 28 December 2007 to 27 December 2010. The 5 most frequently reported nonserious events are listed in [Table 6-4](#). The DEFINITY® post-marketing nonserious AE profile is consistent with the spectrum of events reported during clinical trials. The most frequent spontaneously reported nonserious AEs were back pain (reported at a rate of approximately 1 event per 2,100 vials) and headache (reported at a rate of approximately 1 event per 13,210 vials).

Table 6-4 Most Frequently Reported Nonserious Adverse Events by Preferred Term During Post-Marketing Experience (28 Dec 2007 - 27 Dec 2010)

Preferred Term	Number (Rate) of Events (Denominator ≈ 1,083,000 vials sold)
Back pain	509 (0.04700%)
Headache	82 (0.00757%)
Dyspnoea	61 (0.00563%)
Flushing	54 (0.00499%)
Chest pain	54 (0.00499%)

Of note, the majority of these AEs were spontaneous reports from healthcare providers in relevant clinical settings. These settings include large cohorts of both acute and subacute hospitalized patients, as well as outpatients in hospitals and clinics undergoing resting or rest-stress examinations.

6.3.3 Important Identified Risks

Overall, we have focused attention on the most common serious events, which are cardiopulmonary reactions, hypersensitivity reactions, and convulsions. These are discussed below.

6.3.3.1 Serious Cardiopulmonary Reactions (SCPRs)

Lantheus has defined an SCPR as any case that is fatal or is coded to cardiac arrest, cardiopulmonary arrest, respiratory arrest, myocardial infarction, or a life-threatening ventricular arrhythmia (eg, ventricular fibrillation or ventricular tachycardia). During the time interval for this Briefing Document, 45 patients experienced SCPRs; the events associated with these cases are listed below in descending order of frequency. Even the most commonly reported SCPRs were reported at rates of less than 1 event per 90,000 vials.

Table 6-5 Terms for Serious Cardiopulmonary Reactions Reported During Post-Marketing Experience (28 Dec 2007 - 27 Dec 2010)

Preferred Term	Number (Rate) of Events (Denominator ≈ 1,083,000 vials sold)
Cardiac arrest	12 (0.00111%)
Ventricular tachycardia	11 (0.00102%)
Myocardial infarction	6 (0.00055%)
Death	5 (0.00046%)
Cardio-respiratory arrest	4 (0.00037%)
Supraventricular tachycardia	3 (0.00028%)
Atrial fibrillation	2 (0.00018%)
Bradycardia	2 (0.00018%)
Coma	2 (0.00018%)
Respiratory arrest	2 (0.00018%)
Syncope	2 (0.00018%)
Ventricular fibrillation	2 (0.00018%)
Electrocardiogram abnormal	1 (0.00009%)
Respiratory failure	1 (0.00009%)
Shock	1 (0.00009%)

In cases where comorbid conditions and concomitant medications were reported, it is clear that the majority of patients who experienced SCPRs typically had 1 or more acute or chronic cardiovascular conditions or risk factors that would have predisposed them to future cardiopulmonary events, regardless of testing process. In addition to numerous comorbid conditions, these patients were taking multiple concomitant medications to treat these various conditions, and many of these medications have known adverse effect profiles.

Because of the well known phenomenon of pseudo-complication,^{5, 6} it is expected that serious clinical events will occur in these high-risk populations. At times, these events may occur in close proximity to a test, such as DEFINITY® contrast echocardiography, and therefore create a spurious or questionable association with the test that is unrelated to the mechanism or the cause of the clinical event. Indeed, physicians can be expected to schedule diagnostic tests at the time of major events, for example when patients have echocardiography to aid diagnosis in the setting of acute Myocardial infarction or acute decompensated CHF. These patients are at significant risk of imminent death due to underlying illness. Thus, it is expected that they would be scheduled for diagnostic tests precisely when they are at greatest risk of death.

In addition, we have not been able to clearly associate the incidence of SCPRs with any specific demographic subgroup. Use of the Premier Perspective™ Database permitted matching of demographic profiles and comorbid conditions, and this analysis showed that patients in the ICU who undergo contrast echocardiography are at lower risk for mortality compared to those who did not receive contrast (See [Section 4.1.3](#)).

6.3.3.2 Hypersensitivity and Anaphylactic/Anaphylactoid and Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic and anaphylactoid events, have been reported rarely following DEFINITY® administration. [Table 6-6](#) below lists the events of interest by preferred term during the period of 28 December 2007 – 27 December 2010.

There were 103 patients represented in post-marketing reports of serious hypersensitivity reactions received by LMI. Detailed information on potential sensitization to perflutren has generally not been available in these reports. The 3 most frequently reported serious hypersensitivity reactions were dyspnoea, hypersensitivity, and anaphylactic reaction, reported at rates of approximately 1 event in 51,500 vials, 1 event in 57,100 vials, and 1 event in 71,900 vials of DEFINITY®, respectively. The rates of reported serious hypersensitivity reactions possibly related to DEFINITY® appear to be low, especially for anaphylactic reactions. Similarly low rates are reported from retrospective analyses of large populations by Wei et al.²⁵

By comparison, rates of serious hypersensitivity reactions from other classes of contrast agents are ~ 1/500 to ~ 1/1,000 for iodinated contrast agents^{30,31} and ~ 1/1400 for gadolinium-based contrast agents.³² Therefore, the observed rates of serious hypersensitivity reactions with DEFINITY® compare favorably to rates observed with other imaging modalities.

Table 6-6 All Serious Hypersensitivity, Anaphylactic, and Anaphylactoid Reactions Reported During Post-Marketing Experience (28 Dec 2007 – 27 Dec 2010) by Preferred Term

Preferred Term	Number (Rate) of Events (Denominator ≈ 1,083,000 vials sold)
Dyspnoea	21 (0.00194%)
Hypersensitivity	19 (0.00175%)
Anaphylactic reaction	15 (0.00139%)
Cardiac arrest	11 (0.00102%)
Hypotension	11 (0.00102%)
Respiratory distress	7 (0.00065%)
Anaphylactoid reaction	7 (0.00065%)
Urticaria	6 (0.00055%)
Blood pressure decreased	5 (0.00046%)
Cardio-respiratory arrest	4 (0.00037%)
Throat tightness	4 (0.00037%)
Flushing	4 (0.00037%)
Bronchospasm	3 (0.00028%)
Rash	3 (0.00028%)
Wheezing	3 (0.00028%)
Chest discomfort	2 (0.00018%)
Respiratory arrest	2 (0.00018%)
Angioedema	2 (0.00018%)
Respiratory failure	1 (0.00009%)
Erythema	1 (0.00009%)
Stridor	1 (0.00009%)
Local swelling	1 (0.00009%)
Eyelid oedema	1 (0.00009%)
Localised oedema	1 (0.00009%)
Shock	1 (0.00009%)
Swelling face	1 (0.00009%)
Eye pruritus	1 (0.00009%)
Anaphylactic shock	1 (0.00009%)
Pruritus	1 (0.00009%)
Eye swelling	1 (0.00009%)
Infusion related reaction	1 (0.00009%)
Lip swelling	1 (0.00009%)

Serious hypersensitivity reactions have been reported rarely during post-marketing surveillance. These reactions occurred in both genders and over a wide range of patient ages. Where information was reported, most cases occurred in patients taking 1 or more concomitant medications without a discernibly higher rate in any class or specific medication. While some patients had a prior history of drugs allergies, it is not possible to assess the risk of hypersensitivity in this subgroup because prior history of allergies is inconsistently reported. Since February, 2009, LMI has routinely asked for information on drug allergies, as well as any prior history of allergic reaction to other contrast agents. To date, there is insufficient information to make a credible conclusion about risk, and there does not appear to be a known predictive risk profile for patients who are likely to experience a serious hypersensitivity reaction.

Possible Mechanism and Risk of Hypersensitivity Reactions

Serious hypersensitivity reactions were not observed during pre-approval clinical trials performed with DEFINITY®. In post-marketing experience since 28 December 2007, hypersensitivity reactions have continued to be reported in patients receiving DEFINITY®. The rate of such reactions is monitored on a quarterly basis as part of our signal detection process. With the exception of a “spike” in the rate of hypersensitivity reactions from Q4 2007 to Q3 2008, likely related to increased reporting following addition of the Boxed Warning to the Package Insert, the rate of serious hypersensitivity reactions has remained stable (Figure 6-3).

The mechanism of the serious hypersensitivity reactions remains unclear. However, LMI received laboratory data from a 44-year-old patient who experienced a fatal anaphylactoid reaction (Case 14348080) (see Section 6.3.5), in which markedly elevated levels of tryptase and histamine were detected, suggesting an acute, type I, IgE-mediated reaction. We contacted a number of large centers and determined that it is not routine practice to draw such labs in the setting of acute anaphylactic reactions, where patient treatment is the priority. Review of serious hypersensitivity reactions reveals that time-to-onset is typically within minutes of dosing, which would be consistent with an IgE-mediated reaction. Because such reactions are rare, it is virtually impossible to systematically study this issue. Lantheus study DMP 115-416, a small clinical trial of 32 patients with or without pulmonary hypertension, did not show any meaningful changes in a detailed immunologic panel (including IgE, complement, tryptase, histamine) shortly after dosing. Although no changes were noted, the sample size was too small to draw any meaningful conclusion.

In conclusion, serious hypersensitivity reactions may rarely occur in association with the use of DEFINITY®, as they do with other contrast agents. To date, there are no identified higher-risk patients. The risk of hypersensitivity reactions is clearly described in the product labeling, and sites need to be prepared to treat such patients clinically.

6.3.4 Convulsions

Serious neurological AEs have rarely been reported following DEFINITY® exposure in the post-marketing period. The mechanism of action is unclear, but it could include an allergic-type reaction or vasovagal response. Some events have occurred within 30 minutes of DEFINITY® administration, and a causal relationship cannot be excluded. However, these events are rare and were not seen during pre-approval clinical trials.

All DEFINITY® post-marketing reports from 28 December 2007 to 27 December 2010 of serious events were examined for terms in the Convulsion Standard MedDRA Query (SMQ). The only events included in this SMQ during the interval were convulsion and grand mal convulsion (Table 6-7). The 4 events were reported in 4 separate patients during the interval. Of these 4 cases, 1 patient had a history of seizures. During the 3-year interval, convulsion was reported at a rate of approximately 1 event per 357,100 vials and grand mal convulsion was reported at a rate of approximately 1 event per 1 million vials of DEFINITY®.

Table 6-7 Serious Events in the Convulsion SMQ During Post-Marketing Experience (28 Dec 2007 - 27 Dec 2010) by Preferred Term

Preferred Term	Number (Rate) of Events (Denominator ≈ 1,083,000 vials sold)
Convulsion	3 (0.00028%)
Grand mal convulsion	1 (0.00009%)

6.3.5 Events with a Fatal Outcome (15 April 2008 to 08 Mar 2011)

Since the 2008 Advisory Committee, and up to and including 08 March 2011, spontaneous reports of a total of 10 serious events with fatal outcomes were received (Table 6-8). Serious events occurring within 30 minutes after DEFINITY® administration were noted to be of most interest to the Agency during the last Advisory Committee meeting and have a temporal relationship that increases the probability of relationship to DEFINITY®. Therefore, LMI includes detailed narratives on the 6 cases which occurred within 30 minutes after DEFINITY® administration.

In 2 of these cases, the events occurred shortly after simultaneous dosing with dobutamine during stress echocardiography for known or suspected CAD. Therefore, it is equally plausible that the event was related to dobutamine. These reports describe 5 males and 1 female with ages ranging from 44 to 88 years (mean = 68 years). Four of the fatalities followed a cardiac arrest or cardiorespiratory rest; 2 followed a hypersensitivity reaction. Of the 5 cases where medical history was documented, 5/5 (100%) patients had significant

pre-existing medical conditions, including COPD, cardiac failure, implantable defibrillator, recent acute gastrointestinal bleeding, active deep venous thrombosis, and CABG.

Table 6-8 Events With a Fatal Outcome During the Interval 15 Apr 2008 - 08 Mar 2011

ID #	Source Age Gender	AE Term	Time-to-Onset	Date of Death	Relevant Medical History	Sponsor Causality
Fatalities that occurred within 30 minutes of DEFINITY® administration						
14248165	Spontaneous 54 Male	Cardiac arrest	1 minute after DSE	(b) (6)	COPD, cardiac failure	Possibly related due to short time-to-onset, but equally likely related to DSE
14348080	Spontaneous 44 Male	Anaphylactoid reaction	4 minutes after rest exam	(b) (6) (b) (6)	Nonischemic cardiomyopathy; decreased ejection fraction, 0.5 ppd smoker, alcoholism (24 oz/day), implantable defibrillator, dyslipidemia	Probable causal relationship given short time-to-onset and laboratory evidence of acute anaphylaxis
LMI-2009-00200	Spontaneous 88 Male	Hypersensitivity	Immediately during rest exam (0 min)	(b) (6)	Unknown	Information limited, but given short time-to-onset, causality plausible
LMI-2010-00931	Spontaneous 72 Female	Cardiorespiratory arrest	20 minutes after rest exam; died 5 hours later)	(b) (6)	Recent acute gastrointestinal bleeding, COPD, submandibular mass, metastatic squamous cell cancer, declining respiratory status, and in ICU	Causal relationship cannot be ruled out due to short time-to-onset, but patient had likely alternative etiology as potential cause
LMI-2011-00066	Spontaneous 79 Male	Cardiac arrest	2 minutes (event) after rest exam; died 4 hours later	(b) (6)	Active deep vein thrombosis, recent respiratory arrest, CAD, atrial fibrillation, hypertension, hyperlipidemia, chronic renal failure, edema, and neuropathy	Plausibly related due to short time-to-onset; equally related to underlying condition

ID #	Source Age Gender	AE Term	Time-to- Onset	Date of Death	Relevant Medical History	Sponsor Causality
LMI-2011-00193	Spontaneous 71 Male	Cardiac arrest	Immediately during DSE	(b) (6)	CABG, aortic valve replacement, renal artery stenosis, implantable defibrillator	Plausibly related to DEFINITY® due to time-to-onset, but equally plausibly related to dobutamine (reporting physician believed it was related to natural history and not product).
<u>Fatalities that occurred more than 30 minutes after DEFINITY® administration</u>						
14332704	Spontaneous 70s- 80s Female	Cardiorespiratory arrest	1.5 hours (90 minutes) after rest exam	(b) (6)	Ventricular tachycardia, hypotension, drug hypersensitivity (iodine, contrast media allergy, procainamide, one other)	Not related due to long time-to-onset
LMI-2010-00043	Spontaneous Unknown Age & Gender	Death	45 minutes after rest exam	(b) (6)	Unknown	Not related; time-to-onset > 30 minutes; likely due to alternative etiology
LMI-2011-00117	Investigator-Sponsored Trial 56 Male	Cardiogenic shock; sepsis	7 weeks after rest dosing	(b) (6)	Cardiac failure; bacterial infections (not otherwise specified); dilated cardiomyopathy	Not related to product

ID #	Source Age Gender	AE Term	Time-to-Onset	Date of Death	Relevant Medical History	Sponsor Causality
LMI-2011-00241	Literature report (Kurt, 2009) ³ 78 Male	Cardiac failure	5 hours after rest exam	(b) (6)	Recent acute MI after knee replacement, severe hypotension, recurrent ventricular tachycardia, and severe left ventricular dysfunction	Patient had recent acute MI, severe hypotension, and recurrent ventricular tachycardia in the 24 hours prior to dosing; had echo, without a change in vital signs or ECG. Exam showed severe left ventricular dysfunction. Patient died 5 hours later of continuing severe heart failure. [Not related to DEFINITY®, but rather to underlying medical condition]

Unfortunately, patients in acute care settings such as the ICU are at an elevated risk of mortality. Among critically ill patients in the DMP 115-418 retrospective database study who had a TTE without contrast, 48-hour mortality was nearly 3.1%. Therefore, reports of death in patients who received DEFINITY® in clinical practice are not surprising. In a large population, it would be expected that some fatalities would occur within 30 minutes after DEFINITY® administration. Analysis of the reported deaths shows that timing from dose to event is highly variable, serious comorbidities are common, clinical features of hypersensitivity are apparent in some cases; concomitant medications and procedures complicate the assessment of causality.

The following narratives represent the 6 cases with a fatal outcome that occurred within 30 minutes of DEFINITY® dosing:

Case 14248165: A 54-year-old male patient, hospitalized for heart failure, went into cardiac arrest shortly after receiving DEFINITY® and the maximum dose of dobutamine (50 µg/kg). Resuscitation efforts lasting 40 minutes were unsuccessful. The patient had a prior history of COPD and cardiac failure. It was noted that 1 to 2 months prior to the patient's death, he had a resting perflutren echocardiogram without incident.

In the sponsor's opinion, given the close temporal relationship between dobutamine and DEFINITY® dosing, it is impossible to distinguish between the causal contributions. In addition, some of the AEs seen with dobutamine administration are similar to what has been observed with DEFINITY®. Given the short time-to-onset between dosing and the event, there is a plausible causal relationship to both dobutamine and DEFINITY®.

Case 14348080: A 44-year-old male patient experienced a fatal anaphylactoid 4 minutes after receiving DEFINITY® as part of an evaluation for heart failure. Approximately 3 minutes after dosing, the patient complained of feeling "tingly all over." One minute later, he became cyanotic and appeared to be having seizure-like activity. A paced rhythm was noted on the monitor, but the patient's blood pressure was 60 mmHg palpable. Cardiopulmonary resuscitation (CPR) was begun. He became bradycardic and received atropine and then multiple doses of epinephrine. A full range of resuscitative efforts were unsuccessful. Laboratory measures drawn during resuscitative efforts revealed a markedly elevated histamine level of 11.1 ng/dL (normal is <1 ng/mL), and tryptase of > 200 ng/mL (normal = < 11.4 ng/mL). Complement C3 and C4 were within the reference range. The patient had a prior history of cardiomyopathy with a reduced ejection fraction, dyslipidemia, a ½ packet per day cigarette smoker, and an implantable cardiac defibrillator.

In the sponsor's opinion, given the short time-to-onset, and confirmation of acute anaphylactic laboratory tests, this case is highly likely to be related to DEFINITY®. Based on the laboratory findings, this case appears consistent with an acute, IgE-mediated

hypersensitivity reaction. There was no documented history of allergies to other medications or contrast agents and no indication of increased pre-existing risk.

Case LMI-2009-00200: An 88-year-old male developed itching and hives shortly after receiving DEFINITY® for a rest echocardiogram. The patient received IV diphenhydramine and died shortly thereafter. Intense efforts were made to gather additional information on the case but these efforts were unsuccessful. Medical history, concomitant medications, and risk factors were unavailable.

Information is highly limited on this case, but in the sponsor's opinion, the apparent short time-to-onset between dosing and the hypersensitivity reaction is consistent with a causal relationship to DEFINITY®. Pre-existing medical conditions and potential risk factors are unavailable.

Case LMI-2010-00931: A 72-year-old female who was acutely ill experienced a cardiopulmonary arrest 20 minutes after receiving a second dose of DEFINITY® while in the ICU. She was successfully resuscitated but died approximately 5 hours later. The patient had significant pre-existing comorbidities, had been admitted from another hospital after a 2-week hospitalization, and was admitted with a diagnosis of gastrointestinal bleeding. The patient's respiratory status was declining and, due to marginal oxygenation, she was placed on a BiPAP device. The patient had a medical history of COPD, submandibular mass, metastatic squamous cell carcinoma (primary unknown), hypertension and several packs/day of cigarettes. Concomitant medications included salbutamol, cloinidine, ipratropium bromide, kevaquin, lorazepam, vicodin, pantoprasole sodium, methylprednisolone, verapamil, ondansetron, and hydralazine. The admission hematocrit was 21.3 and on the day of the event it was 24.3.

In the sponsor's opinion, this event is related to underlying disease and not to DEFINITY®. The patient's respiratory status was marginal and the event occurred 20 minutes after the second dose of DEFINITY®. In other words, she experienced no AE following the first dose. In addition, she was taking a number of concomitant medications to treat her chronic and acute conditions.

Case LMI-2011-00066: A 79-year-old male experienced a cardiac arrest 2 minutes after receiving DEFINITY® while in the ICU. Despite being successfully resuscitated, he died approximately 4 hours after the event. The patient had experienced a spontaneous respiratory arrest 6.5 hours prior to the event and prior to receiving DEFINITY®. The patient had a known deep venous thrombus (positive d-dimer of > 20), and the reporting physician believed that the respiratory arrest may have been due to a pulmonary embolus. One week earlier, outpatient pre-operative testing revealed CAD (50% stenosis of the right coronary artery, diagonal branch of the left anterior descending artery and posterior descending artery,

and 90% stenosis of the posterolateral artery). The patient's past medical history also included chronic renal failure (on hemodialysis), hyperlipidemia, hypertension, neuropathy, edema, diastolic heart failure, and atrial fibrillation. The reporting physician saw the echocardiograph and said that shortly after administration, he saw both ventricles dilate, and then the patient went into asystole. The patient was resuscitated and regained a pulse after 6 minutes. Multiple pressor agents were increased to maximal rates, and approximately 4 hours after the initial cardiac arrest, the patient again went into asystole and died.

Given the 2-minute time-to-onset of the events, it is impossible to rule out a possible causal relationship to DEFINITY®. However, the patient had significant medical comorbidities, including a recent history of spontaneous respiratory arrest, possibly due to a pulmonary embolus, which make it likely that underlying comorbidity may have significantly contributed to the outcome. The observation of right ventricular dilation shortly after dosing is consistent with a massive pulmonary embolus, however, left ventricular dilation is not.

Case LMI-2011-00193: A 71-year-old male patient died of cardiac arrest during a dobutamine stress test to check the functioning of his implantable cardioverter defibrillator and for evaluation of his aortic valve. Shortly after receiving the dobutamine, the patient went into cardiac arrest, coded, and died. His past medical history was significant for coronary artery bypass, aortic valve replacement, renal artery stenosis, and an implantable cardioverter defibrillator.

The reporting physician believed that the event was related to natural history of disease and not to DEFINITY®. In the sponsor's opinion, given the short time-to-onset of the event to dosing, it is impossible to rule out a possible causal relationship to DEFINITY®, dobutamine, or the natural history of the patient's cardiovascular disease.

6.4 Data Monitoring Committee (DMC)

Lantheus voluntarily assembled an independent DEFINITY® Post-Marketing DMC in 2009. The Committee is chaired by a cardiologist, with additional members who specialize in epidemiology and clinical immunology.

The first meeting occurred on 10 December 2009 at Brigham and Women's Hospital. The materials reviewed by the committee in advance of the meeting included a presentation on the history of the product including safety and regulatory history, the complete MedWatch forms for all SAE cases received in 2009 to date (as well as those received in 2008 for comparison), a chart and graph of the historic quarterly rate of serious and nonserious AE cases to date, completed Clinical Study Reports for 2 post-marketing safety studies (DMP 115-415, DMP 115-418), and a presentation done by a lead investigator for 1 of these studies at ASE. The presentation on the safety and efficacy history of DEFINITY® was

given and the rest of materials were discussed at the meeting and the committee concluded that no adverse safety signals were identified.

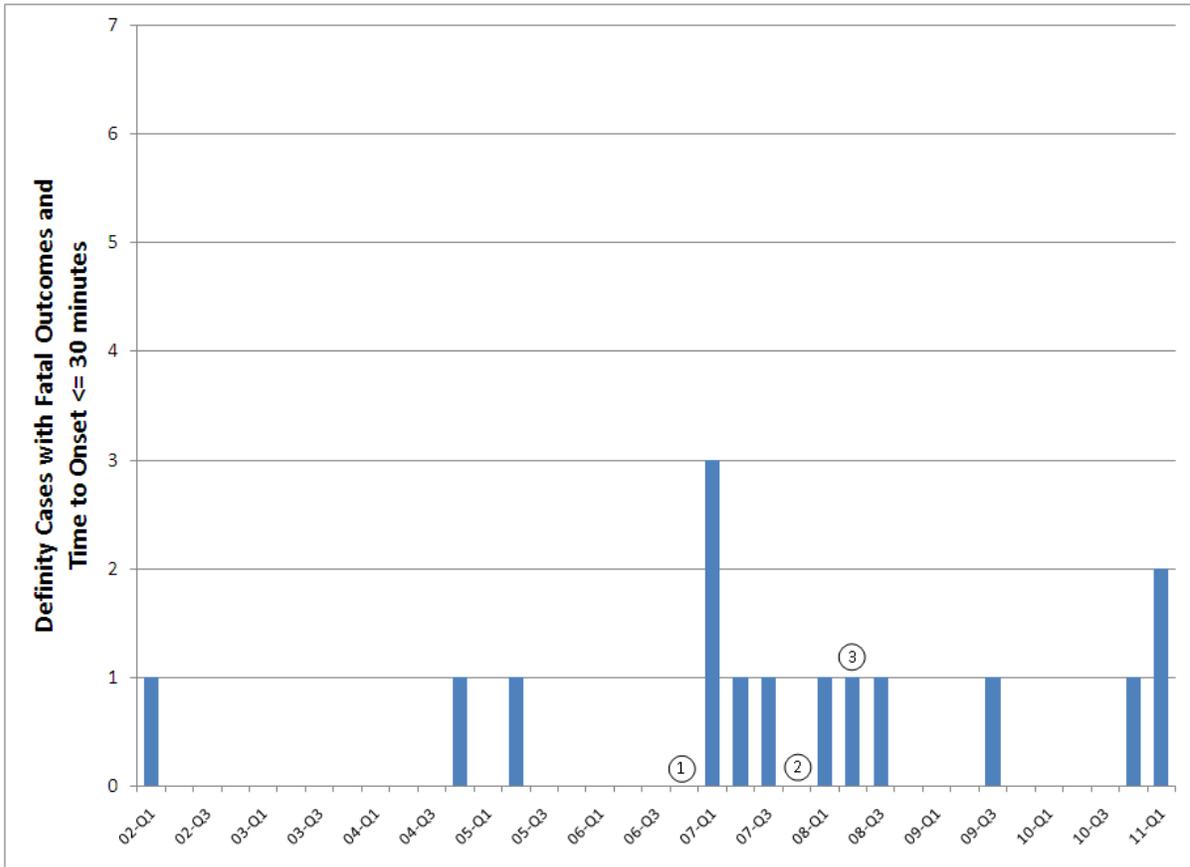
The next meeting occurred on 30 June 2010 by teleconference. The materials discussed by the committee included an update on the pharmacovigilance (PV) system at LMI, formation of a MSRT at LMI, review of all MedWatch forms for all SAE cases received since the last meeting, a chart and graph of the historic quarterly rate of serious and nonserious AE cases to date, and a completed Clinical Study Report for a post-marketing safety study in patients with pulmonary hypertension (DMP 115-416). At the conclusion of the meeting, the Chairman and DMC members agreed that no new safety signals were identified, and that they had no safety recommendations concerning the use of the product.

6.5 Lantheus Signal Detection Activities

In addition to the review and analysis of individual cases, LMI also performs a quarterly signal detection process for DEFINITY®. This process utilizes internal sales figures for product use (denominator) and reports of AEs from an output of the validated ARISg safety database (numerator) to assess rates of AE during a particular time interval. The rate is then compared to an historical standard and variance from the expected rate is assessed. This rate assessment is done for SAEs, nonserious AEs, adverse events of special interest (AESIs), and other events as needed. If the rate is more than 3 SD above the historical mean, this constitutes a potential signal. In addition to identification and analysis of AE and SAE rates, the signal detection process summarizes any relevant studies completed during the interval, reviews any published literature relevant to safety, and identifies important cases for discussion. If the conclusion is that there is a possible adverse safety signal, then this information is shared with the MSRT, a committee consisting of senior members of relevant LMI departments. At a minimum, the MSRT meets on a quarterly basis.

Serious post-marketing cases with a time-to-onset within 30 minutes of DEFINITY® administration that resulted in fatality are presented in [Figure 6-1](#), reported on a quarterly basis since product launch. In the majority of quarters, no fatalities were reported spontaneously or noted during other surveillance activities. The maximum quarterly number of fatalities was 3, reported in Q1 2007, immediately following the November 2006 Dear Healthcare Provider Letter. Subsequent fatality reports to LMI GPV were clustered in the period between Q1 2007 and Q3 2008. In May 2008, a Dear Healthcare Provider Letter announced the following changes to the 2007 Boxed Warning 1) removal of the contraindications and 2) restriction of the required 30-minute monitoring to patients with pulmonary hypertension and acute cardiac and pulmonary conditions. Rates of fatalities have decreased and stabilized since Q3 2008. This pattern of reporting is repeated for all types of serious cases.

Figure 6-1 Fatal Post-Marketing Cases Within 30 Minutes of DEFINITY® Administration by Quarter

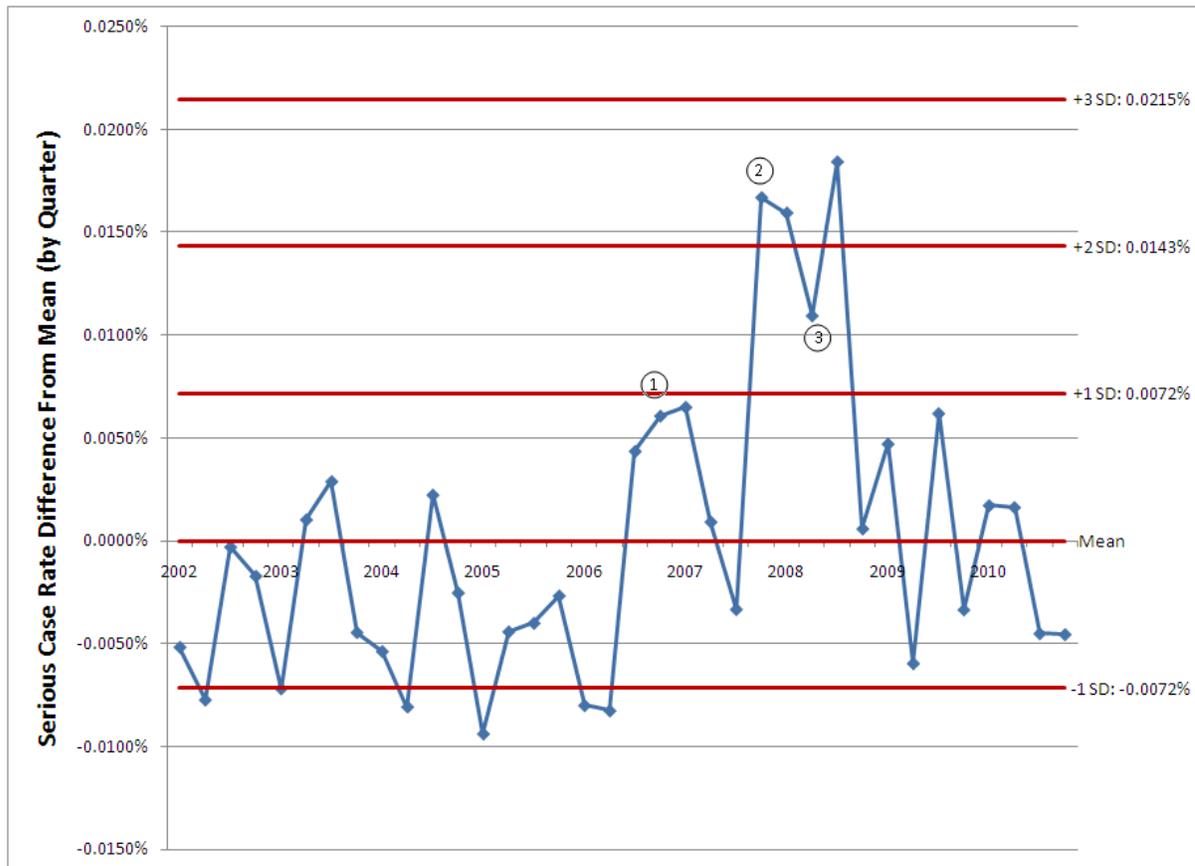


- ¹ 30 November 2006 - Dear Healthcare Provider Letter announced potential revisions to the US Package Insert regarding serious hypersensitivity and serious neurological reactions.
- ² 10 October 2007 - Dear Healthcare Provider Letter announced Boxed Warning requirements for 30-minute monitoring in all patients and 5 contraindications in patients with serious underlying cardiac and pulmonary conditions.
- ³ 06 May 2008 - Dear Healthcare Provider Letter announced removal of the contraindications and revisions included in the 10 October 2007 Boxed Warning to require 30-minute monitoring only in patients with pulmonary hypertension and acute cardiac and pulmonary conditions.

Signal detection graphs are provided for SAEs (Figure 6-2), anaphylactic reactions (Figure 6-3), serious events in the Convulsion SMQ (Figure 6-4), and SCPRs and fatal cases (Figure 6-5). These graphs were obtained by using current sales (denominator) data and SAE data from the safety database, using a difference from the historical means. The shapes of

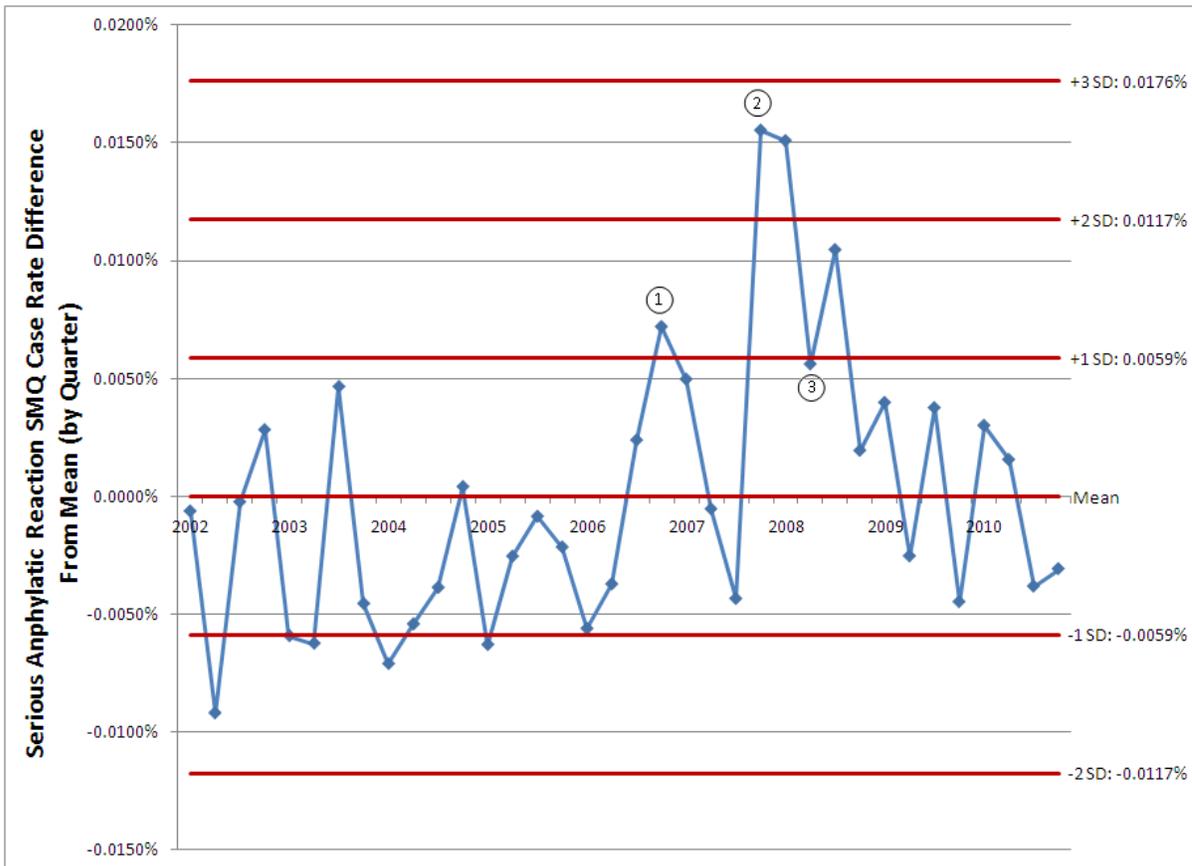
the graphs are similar, showing a “spike” in late 2007 and most of 2008. It is likely that the spike was related to increased awareness and enhanced reporting around publication of the Boxed Warning. As can be seen in each of the graphs, the rates of these SAEs have decreased and stabilized over the past 1.5 to 2 years.

Figure 6-2 Serious Case Rate Difference From Mean by Quarter



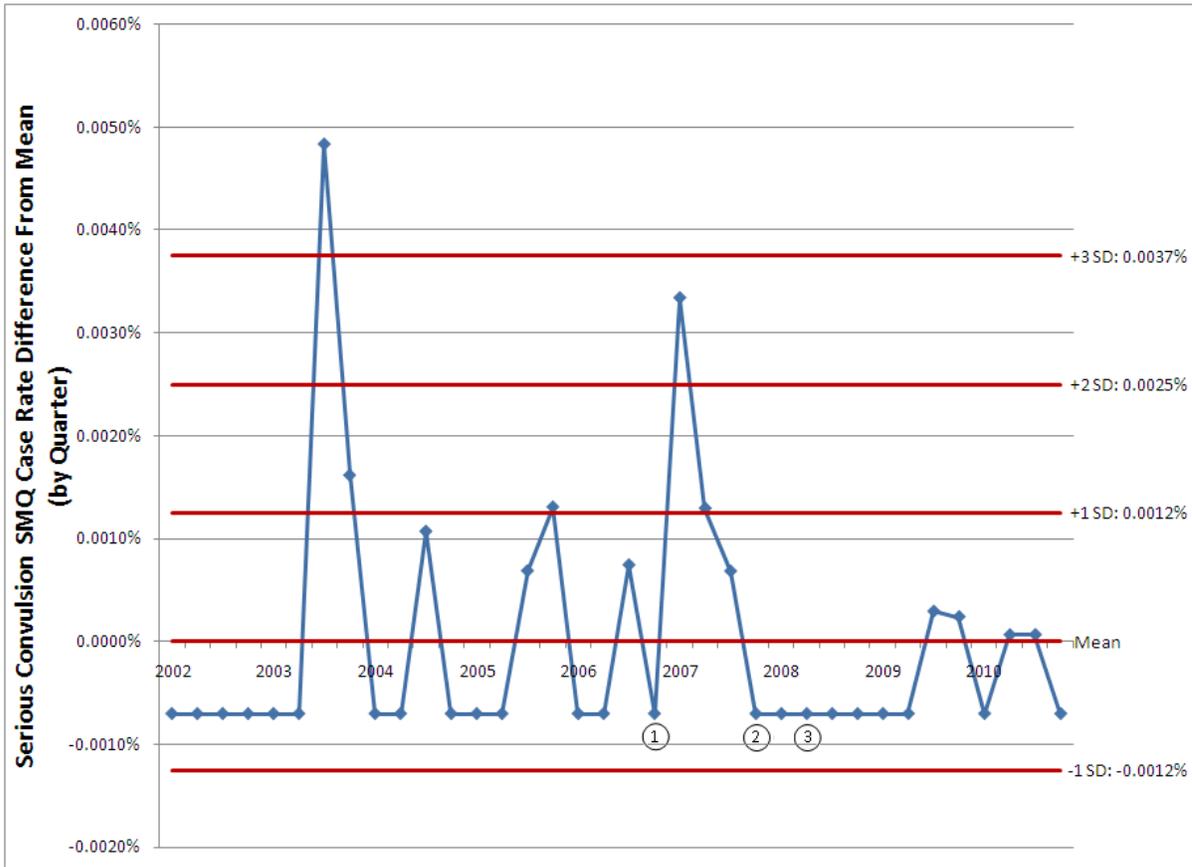
- ¹ 30 November 2006 - Dear Healthcare Provider Letter announced potential revisions to the US Package Insert regarding serious hypersensitivity and serious neurological reactions.
- ² 10 October 2007 - Dear Healthcare Provider Letter announced Boxed Warning requirements for 30-minute monitoring in all patients and 5 contraindications in patients with serious underlying cardiac and pulmonary conditions.
- ³ 06 May 2008 - Dear Healthcare Provider Letter announced removal of the contraindications and revisions included in the 10 October 2007 Boxed Warning to require 30-minute monitoring only in patients with pulmonary hypertension and acute cardiac and pulmonary conditions.

Figure 6-3 **Serious Anaphylactic Reaction Case Rate Difference From Mean by Quarter**



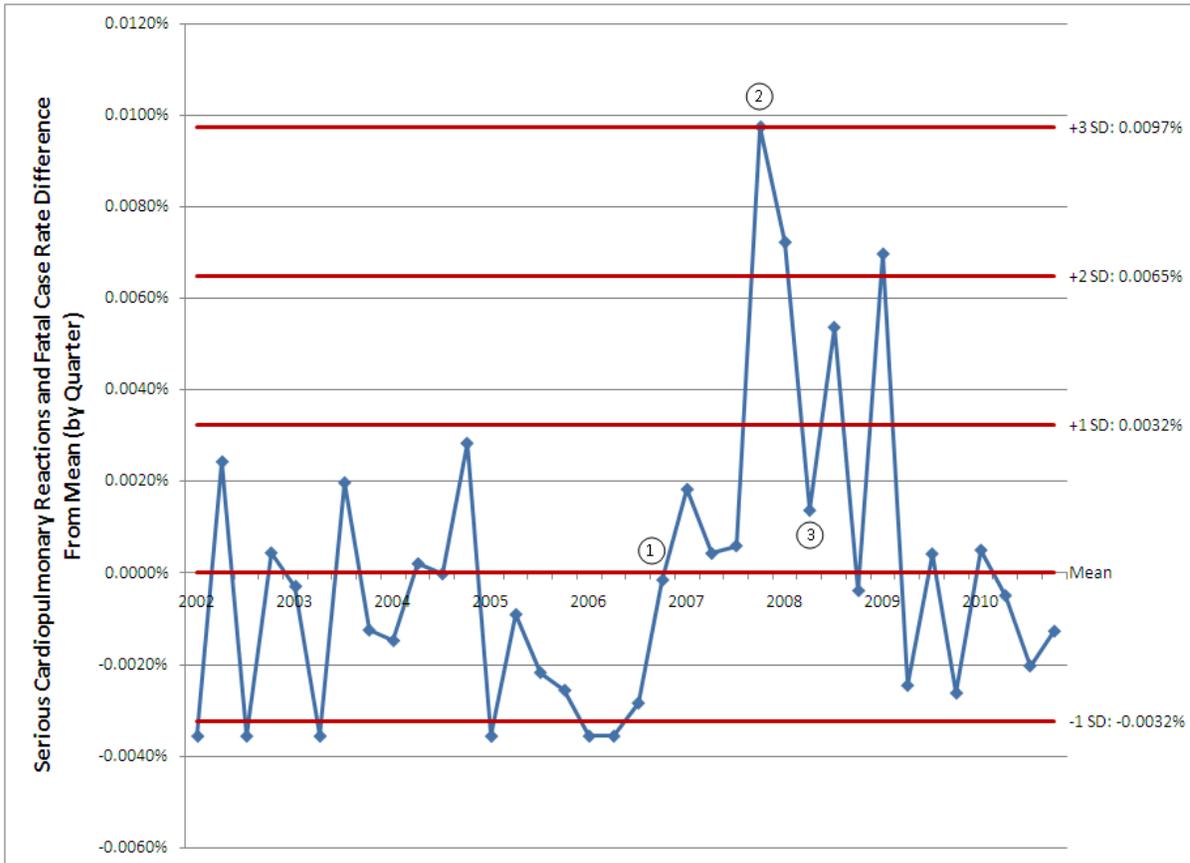
- ¹ 30 November 2006 - Dear Healthcare Provider Letter announced potential revisions to the US Package Insert regarding serious hypersensitivity and serious neurological reactions.
- ² 10 October 2007 - Dear Healthcare Provider Letter announced Boxed Warning requirements for 30-minute monitoring in all patients and 5 contraindications in patients with serious underlying cardiac and pulmonary conditions.
- ³ 06 May 2008 - Dear Healthcare Provider Letter announced removal of the contraindications and revisions included in the 10 October 2007 Boxed Warning to require 30-minute monitoring only in patients with pulmonary hypertension and acute cardiac and pulmonary conditions.

Figure 6-4 **Serious Events in the Convulsion SMQ Case Rate Difference From Mean by Quarter**



- ¹ 30 November 2006 - Dear Healthcare Provider Letter announced potential revisions to the US Package Insert regarding serious hypersensitivity and serious neurological reactions.
- ² 10 October 2007 - Dear Healthcare Provider Letter announced Boxed Warning requirements for 30-minute monitoring in all patients and 5 contraindications in patients with serious underlying cardiac and pulmonary conditions.
- ³ 06 May 2008 - Dear Healthcare Provider Letter announced removal of the contraindications and revisions included in the 10 October 2007 Boxed Warning to require 30-minute monitoring only in patients with pulmonary hypertension and acute cardiac and pulmonary conditions.

Figure 6-5 **Serious Cardiopulmonary Reactions and Fatal Case Rate Difference From Mean by Quarter**



- ¹ 30 November 2006 - Dear Healthcare Provider Letter announced potential revisions to the US Package Insert regarding serious hypersensitivity and serious neurological reactions.
- ² 10 October 2007 - Dear Healthcare Provider Letter announced Boxed Warning requirements for 30-minute monitoring in all patients and 5 contraindications in patients with serious underlying cardiac and pulmonary conditions.
- ³ 06 May 2008 - Dear Healthcare Provider Letter announced removal of the contraindications and revisions included in the 10 October 2007 Boxed Warning to require 30-minute monitoring only in patients with pulmonary hypertension and acute cardiac and pulmonary conditions.

In conclusion, the safety profile for DEFINITY® in terms of SAEs and AESIs stabilized over the past 1.5 to 2 years. There is no evidence of a new or worsening safety signal during the time interval for this Briefing Document. Lantheus will continue to perform quarterly signal detection activities with DEFINITY®, indefinitely as clinically indicated.

7 OVERALL CONCLUSIONS

Both Lantheus-sponsored clinical trials and independent peer-reviewed publications support the safety, efficacy, and clinical utility of DEFINITY[®] in accordance with professional society practice guidelines. Furthermore, DEFINITY[®] has an established safety profile in a broad range of acute cardiopulmonary conditions where diagnostic imaging without contrast often is not possible.

In post-marketing safety surveillance, rare serious and fatal events have been reported within 30 minutes of DEFINITY[®] administration. Detailed case information gathered through the LMI PV system indicates that some of these events may result directly from administration of DEFINITY[®] and/or other concomitant medications administered around the time of echocardiography (eg, dobutamine). Other AEs may stem from progression of underlying serious illness at the time of DEFINITY[®] administration (ie, pseudo-complications).^{5,6} Very rare AEs appear to have an allergic nature and may be related to DEFINITY[®].

No subgroup of patients appears to be at particular risk for these serious events. The rates of these reactions have remained stable - they occur at approximately the same rate as prior to the implementation of the Boxed Warning in October 2007. An independent post-market safety DMC has convened twice for periodic safety data review from all available sources and has concluded that no additional safety risks have emerged since 2008.

The presence of the Boxed Warning has significantly reduced the use of DEFINITY[®], possibly in cases where contrast administration would be considered appropriate or even necessary. Current utilization rates are ~1.5%, which is well below the estimated frequency of suboptimal echocardiograms in the US (15% to 20%). Current use is also less than what would be expected if professional society-based guidelines, accreditation standards, and clinical use consensus statements were followed (~ 15%, higher in the ICU setting).⁷⁻⁹ In some cases, patients may have been steered toward alternative imaging procedures that are associated with rates of SAEs and mortality that exceed the rates associated with ultrasound contrast echocardiography.¹⁰

The efficacy and safety of DEFINITY[®] have been established in a broad range of stable and unstable patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. This position is supported by current ASE guidelines and ICAEL accreditation standards.⁷⁻⁹ Lantheus believes that there is clinical need for DEFINITY[®] in acute settings, or when significant heart failure, arrhythmias, or other cardiovascular disease is evaluated. Examples of acute settings where use of DEFINITY[®] can aid diagnosis include:

- Acute MI (both ST-elevation and non-ST-elevation), where echocardiography is helpful for differential diagnosis in an emergency setting and for accurate risk assessment within 48 hours when patients are still unstable. This is because DEFINITY® visualizes the left ventricular border and permits the evaluation of left ventricular systolic function. This information guides therapeutic intervention.
- Acute heart failure, where patient treatment and proper risk stratification depend on the accuracy of assessments of left ventricular function, left ventricular ejection fraction, left ventricular volumes, and characterization of wall motion abnormalities.
- In the setting of mechanical ventilation, patients are frequently difficult to image because of the ventilation, their immobility, and the acuity of their disease. These patients with hemodynamic compromise require immediate assessments of regional and global left ventricular structure and function and possible complications such as apical thrombus and false aneurysm to determine whether their condition is due to cardiac disease or some noncardiac cause. This is mandatory, now that expensive and invasive right-heart catheterization techniques have been largely abandoned.
- Pulmonary hypertension, where patients with significant pulmonary disease or heart failure require accurate detection of right ventricular and left ventricular abnormalities and/or contrast-enhanced assessment of the tricuspid regurgitation jet to quantify pulmonary artery pressure.

These settings were specifically investigated by Lantheus in 2 FDA-required Post-Approval studies: DMP 115-418, an acute (ICU) care retrospective database study, and the DMP 115-416 study in patients with pulmonary hypertension ([Section 4.1.3](#) and [Section 4.1.2](#), respectively). In addition, a third required Post-Approval study (DMP 115-415) examined routine clinical use of DEFINITY® ([Section 4.1.1](#)). In every study performed, there was no identifiable additional risk associated with the use of DEFINITY®, even in patients who were highly compromised prior to DEFINITY® administration and who, in some cases, were clinically unstable. However, statistically and clinically significant incremental benefits, in terms of reductions in 48-hour and hospital stay all-cause mortality, were observed when echocardiography with DEFINITY® was compared to the noncontrast group in the DMP 115-418 study. In this study, analyses of 21 of 23 patient subgroups (comorbidities) found that the percentage of patients who died was lower in the DEFINITY® group than in the noncontrast group. Patients with acute MI, mechanical ventilation, and pulmonary hypertension were among those with statistically significantly lower death rates in the DEFINITY® group than in the noncontrast group.

Several potential mechanisms by which patient mortality might have been improved in the contrast group in the DMP 115-418 study were identified in the recent publication by Kurt et al.³ Kurt et al reported on a prospective study in patients with technically difficult echocardiographic studies who received DEFINITY® as part of routine clinical diagnostic

care, according to the ASE Consensus Statement.⁷ The authors found statistically significant ($p < 0.0001$) reductions in the percent of uninterpretable studies and the percent of technically difficult studies with use of contrast. Use of DEFINITY® was also associated with an increase in the mean number of endocardial wall segments visualized from 11.6 without contrast in the suboptimal baseline studies to 16.8 of 17 segments visualized with DEFINITY®. The use of DEFINITY® also led to additional diagnostic tests being avoided in 32.8% of patients, drug management alteration in 10.4% of patients, and an overall change in management in 35.6% of patients. A left ventricular thrombus was suspected in 35 patients and was definite in 3 patients before use of DEFINITY®. After use of contrast, only 1 patient had a suspected thrombus and 5 additional patients were identified as having thrombus ($p < 0.0001$). The effect of contrast increased with worsening quality of the unenhanced study, especially in ICUs among critically ill patients. This had a significant impact on patient management decisions. Adjustments in patient management decisions could reasonably be expected to have a salutatory effect on clinical outcomes.

In summary, post-market safety surveillance through multiple mechanisms has not revealed any change in the safety profile for DEFINITY® in the interval 3 years. Rare deaths and uncommon SAEs continue to occur at extremely low and consistent rates. Review of individual cases and overall trends has not revealed any clear pattern of risk or specific patient subgroups that are at higher risk.

Lantheus believes that new data obtained from clinical trials and post-market surveillance since 2008 continue to demonstrate a favorable benefit-risk profile. Lantheus believes that the risks of DEFINITY® are well characterized and that the product offers a clinically important, immediate point-of-care, and nonradioactive improvement when noncontrast echocardiographic ultrasound imaging is suboptimal.

Based on a stable safety profile and results from post-market safety studies conducted in patients with serious comorbidities, as outlined above, Lantheus believes the use of a box warning should be reconsidered.

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