

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021064Orig1s011

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 21-064	NDA Supplement #: S- 011	Efficacy Supplement Type SE- 8
Proprietary Name: Definity Established/Proper Name: Perflutren Lipid Microspheres Dosage Form: Parenteral Strengths: Variable		
Applicant: Lantheus Medical Imaging Inc.		
Date of Receipt: September 29, 2009		
PDUFA Goal Date: July 29, 2011 (first Cycle) October 24, 2011 (2nd Cycle)		Action Goal Date (if different): Same
Proposed Indication(s): For use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of left ventricular endocardial border.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
(b) (4)	<ul style="list-style-type: none"> • Safety data (to update boxed warning , removing monitoring and/or observation of patients
PMR data for the same product	<ul style="list-style-type: none"> • Removal of Cautionary statement in indications section • Summary of PMR studies in Post Marketing Section • Updates in Clinical Pharmacology, warnings and precaution, and Adverse reaction sections

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Answer: This application is a supplemental NDA requesting a change of the indication statement. The referenced product is the proposed product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "**NO**", proceed to question #5.

If "**YES**", list the listed drug(s) identified by name and answer question #4(c).

Definity

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

N/A-Referenced drug product is proposed drug product

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

Answer: This application provides for the removal of the following statement from Definity’s currently approved labeling: ‘The safety and efficacy of DEFINITY® with exercise stress or pharmacologic stress testing have not been established.’

The change results in the following indication statement:

Activated Definity® injectable suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of left ventricular endocardial border.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including*

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If **“YES”** *and* there are no additional pharmaceutical alternatives listed, proceed to question #12.

If **“NO”** *or* if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If **“NO”**, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of

approval

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/s/

FRANK A LUTTERODT
11/03/2011

INTRODUCTION

On September 29, 1010, Lantheus Medical Imaging submitted a prior approval labeling supplement to reformat the Definity (perflutren lipid microsphere) labeling in accordance with the Physician's Labeling Rule (PLR) to the Division of Medical Imaging (DMIP). Definity is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve delineation of the left ventricular endocardial border. In 2008, because of concerns regarding serious cardiopulmonary reactions associated with use of Definity that included fatalities, a boxed warning was added to the labeling.

DMIP consulted the Pediatric and Maternal Health Staff's Maternal Health Team (MHT) on May 4, 2011 to review the pregnancy section of the Sponsor's proposed labeling. This review includes revisions to the Sponsor's proposed Pregnancy and Nursing Mothers subsections of Definity labeling.

BACKGROUND

Definity (perflutren lipid microsphere) is an ultrasound contrast agent initially approved in 2001. Definity is composed of octafluoropropane (OFP) gas encapsulated in a phospholipid shell. OFP is a gas that is not metabolized and the phospholipid components are metabolized into free fatty acids. OFP gas is not detectable in patients after 10 minutes in blood or expired air. The mean half life of OFP gas is 1.3 minutes in healthy patients.¹

The approved indication is for use in patients with suboptimal rest echocardiograms. The presence of microbubbles (OFP gas) provides echoes necessary for ultrasound imaging.² Definity is used to further opacify the left ventricular chamber and improve the delineation of the left ventricular endocardial border. This increases the accuracy of echocardiography for detecting potential coronary artery disease.³ Serious cardiopulmonary reactions such as cardiac or respiratory arrest, arrhythmias, hypotension, and cardiac ischemia have been noted after administration of Definity. For this reason, high risk patients are monitored for 30 minutes after administration.

This review provides revisions to the Sponsor's proposed Pregnancy and Nursing Mothers subsections of Definity Labeling.

REVIEWED MATERIALS

Sponsors Proposed Pregnancy and Nursing Mothers Labeling

¹ Definity labeling

² AIUM Consensus Report on Potential Bioeffects of Diagnostic Ultrasound, Executive Summary. *J Ultrasound Med.* 2008;27:503-515.

³ Gabriel RS, Smyth YM. et al. Safety of Ultrasound Contrast Agents in Stress Echocardiography. *Am J Cardiol.* 2008;102:1269-1272.

8 USE IN SPECIFIC POPULATIONS

(b) (4)



DISCUSSION

Definity (perflutren lipid microsphere) is an ultrasound contrast agent initially approved in 2001, that is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve delineation of the left ventricular endocardial border. The Pediatric and Maternal Health Staff 's Maternal Health Team (MHT) agrees with the current pregnancy category B based on negative developmental toxicity studies in animals and no adequate and well controlled studies on the use of Definity during human pregnancy.

With regards to the Nursing Mothers subsection of labeling, the MHT noted the drug's very short half life and determined that if nursing mothers pump and discard breast milk once after receiving Definity, infant drug exposure through human milk is highly unlikely. This reviewer discussed this issue with Christy John, PhD of Clinical Pharmacology, who concurred with this assessment.

The MHT has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. The Pregnancy and Nursing Mothers section of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus, and/or infant. PMHS-Maternal Health labeling recommendations not only comply with current regulations but also incorporate "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, the required regulatory language for the designated pregnancy category, and, when available, outcomes of studies conducted in pregnant women and studies conducted in animals. The paragraphs that follow provide more detailed descriptions of the available human and animal data and appropriate clinical information that may affect patient management.

RECOMMENDATIONS

1. Definity should be labeled pregnancy category B.
2. Nursing mothers should be advised to pump and discard breast milk once after receiving Definity.
3. Below are the MHT's recommended revisions to the Sponsor's proposed labeling. A track changes versions has been included in Appendix A.

PMHS – Maternal Health Labeling Recommendations

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of DEFINITY in pregnant women. Reproduction studies performed in rats and rabbits at doses up to 24 and 15 times the human dose based on body surface area (in rats and rabbits respectively) revealed no evidence of impaired fertility or harm to the fetus due to DEFINITY. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether DEFINITY is excreted in human milk. Based on the rapid clearance of this drug, advise nursing mothers to pump and discard breast milk once after treatment. *[see Pharmacokinetics (12.3.3)]* Because many drugs are excreted in human milk, caution should be exercised when DEFINITY is administered to a nursing mother.

Appendix A

Revisions for Definity Pregnancy and Nursing Mothers Labeling (with track changes)



(b) (4)

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/s/

UPASANA BHATNAGAR
06/15/2011

LISA L MATHIS
06/28/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: 6/13/2011
To: Frank Lutterodt, Regulatory Project Manager
Division of Medical Imaging Products
From: James Dvorsky, Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications
Subject: Comments on draft labeling (Package Insert) for NDA 21064,
Definity (Perfluten Lipid Microspheres) injectable suspension

In response to your labeling consult request on March 1, 2011, we have reviewed the draft Package Insert for Definity and offer the following comments. Note that these comments are based upon the 6-8-11 label version.

Package Insert Labeling:

Section	Statement	Comment
Table 6.1		(b) (4)
8.4 Pediatric Use		

14.2 Post-Market



(b) (4)

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/s/

JAMES S DVORSKY
06/13/2011

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/s/

JEANINE A BEST
06/09/2011

HARI C SACHS
06/10/2011
I agree with the recommendations in this consult.

LISA L MATHIS
06/10/2011



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 16, 2011

From: Suchitra Balakrishnan, MD., Ph.D.

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Frank Lutterodt
RPM, DMIP

Subject: DCRP consult to NDA 21-064

This memo responds to your consult to us dated April 28, 2011 regarding ECG findings with ultrasound contrast agents Definity and Optison, sponsored by Lantheus medical Imaging Inc.. The QT-IRT received and reviewed the following materials:

- Your consult
- CSRs for studies DMP 115-415, DMP 115-416, GE-191-504
- DMP 115-504: A summary of sponsor clinical trial experience with Definity.

DCRP Comments for DMIP

- The ECG findings submitted were inconclusive because of the following reasons:
 - These were trials where single ECGs were recorded with no central over-read. ECGs were not collected at Tmax (30-40 seconds post-dose). Hence any mean changes reported are unreliable. Even large ECG interval effects (> 20 ms) could only be excluded if ECGs were collected around Tmax, which is not the case here.
 - Typically, for ECG findings from phase 2 and 3 clinical studies we only report categorical data (absolute values over 500 ms and 60 ms change from baseline) in control vs. study drug in the PI. Again, the categorical data provided by the sponsor with this submission is non-informative since Tmax was not captured.

- Since the drug is pro-arrhythmic because of other mechanisms (as per warning section in the PI on mechanical indices etc.) and the concern for anaphylactoid reactions, the drug will continue to be administered with intensive cardiac monitoring and therefore we do not believe that a TQT study per the ICH E14 guidelines to quantify QT effects will be necessary from a safety standpoint. Moreover, the agent has a short half-life and is being administered by personnel trained in arrhythmia management.

BACKGROUND

DMIP has consulted DCRP to comment on the relationship (if any) of reported ECG changes to administration of the ultrasound contrast agents Definity (Perflutren Lipid Microsphere) and Optison (Perflutren Protein-Type A Microspheres) Injectable Suspensions. The division has requested review of ECG findings from post marketing studies and integrated clinical trial summaries with these agents.

Both contrast agents have a boxed warning for serious cardiopulmonary reactions including fatalities which have occurred during perflutren-containing microsphere administration. As per the *PI*, the risk for these reactions may be increased among patients with pulmonary hypertension or unstable cardiopulmonary conditions and intensive monitoring of these patients is recommended. Having cardiopulmonary resuscitation personnel and equipment readily available prior to administration and monitoring all patients for acute reactions is advised. Post-marketing reports of fatal cardiac or respiratory arrest, hypotension, supraventricular and ventricular arrhythmias, respiratory distress or decreased oxygenation are included in the *PI*. Reports also identified neurologic reactions (loss of consciousness or convulsions) as well as anaphylactoid reactions. In addition, there is a warning statement that high ultrasound mechanical index values may cause microsphere cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias. The safety of activated DEFINITY[®] at mechanical indices greater than 0.8 and with end-systolic triggering has not been evaluated.

QTc Prolongation information in current PI:

“ECG parameters for doses up to 10 µL/kg were monitored in 221 subjects at multiple time points from 1 hour to 72 hours after the first bolus injection. In the 221 subjects, QTc prolongations of >30 msec were noted in 64 (29%) subjects. Forty-six out of 64 subjects with QTc prolongations were further evaluated and 39% (18/46) showed associated cardiac rhythm changes. The effects of concomitant drugs were not studied.”

Reviewer’s Comment: These findings are inconclusive as Tmax was not captured. Typically we report outliers with absolute change over 500 ms or over 60 ms change from baseline.

Product Information and Clinical Pharmacology

Source PI approved April 2008

The DEFINITY[®] vial contains components that upon activation yield perflutren lipid microspheres, a diagnostic drug that is intended to be used for contrast enhancement during the indicated echocardiographic procedures. The vial contains a clear, colorless hypertonic liquid, which upon activation with the aid of a Vialmix[®], provides a homogeneous, opaque, milky white injectable suspension of perflutren lipid microspheres. The suspension of activated DEFINITY[®] is

administered by intravenous injection. The perflutren lipid microspheres are composed of octafluoropropane encapsulated in an outer lipid shell.

Human pharmacokinetics information is not available for the intact or degassed lipid microspheres. The pharmacokinetics of octafluoropropane gas (OFP) were evaluated in healthy subjects (n=8) after the IV administration of activated DEFINITY® at a 50 µL/kg dose. OFP was not detectable after 10 minutes in most subjects either in the blood or in expired air. OFP concentrations in blood were shown to decline in a mono-exponential fashion with a mean half-life of 1.3 minutes in healthy subjects.

Optison

Source: PI approved May 2008

OPTISON™ (Perflutren Protein-Type A Microspheres Injectable Suspension, USP) is a suspension of microspheres of human serum albumin with perflutren for contrast enhancement during the indicated ultrasound imaging procedures.

Neither the pharmacokinetics of the intact microspheres or of the human albumin component have been evaluated in humans. Following a single intravenous dose of 20 mL OPTISON to 10 healthy volunteers (5 men and 5 women), most of the perflutren was eliminated through the lungs within 10 minutes. The recovery was 96% ± 23% (mean ± SD), and the pulmonary elimination half-life was 1.3 ± 0.69 minutes (mean ± SD). The perflutren concentration in expired air peaked approximately 30-40 seconds after administration.

Clinical experience:

[Redacted text block] (b) (4)

[Redacted text block] (b) (4)



ECG findings

All ECG parameter data presented rely on readings conducted as specified in the original clinical trials. A variety of approaches was used, but information from any manual over-reads was not collected on CRFs. Since these were single ECGs with no central over-read, mean changes reported are unreliable. Timing of ECGs post-treatment is variable.





DMP 115-415: A safety registry of 1053 patients who underwent an echocardiogram with Definity in routine medical practice. In study DMP 115-415, patients underwent echocardiograms with Definity either at rest or in stress. Roughly half of the patients underwent echocardiograms in stress. 12-lead ECGs were obtained prior to the echocardiogram with Definity and also at 5 minutes, 15 minutes, and 30 minutes after administration. ECG interpretation and abnormalities are provided and summarized. ECG adjudication was performed at the clinical study sites by the Investigator. Only ECG abnormalities are reported in the CSR. No ECG interval data are available.

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

Table 14.3.5.3a
Summary and Change from Baseline in 12-Lead Electrocardiograms - Overall
(Safety Population)

Parameter	Visit	N	Time Point		Change		
			Mean (SD)	Min - Max	N	Mean (SD)	Min - Max
HR (bpm)	BASELINE	32	73.2 (15.02)	50 - 110			
	DAY 1	30	71.0 (11.84)	52 - 100	30	-1.3 (13.46)	-49 - 18
QT (msec)	BASELINE	29	401.7 (92.16)	40 - 560			
	DAY 1	28	410.4 (84.07)	32 - 560	27	5.4 (41.31)	-108 - 85
QTc(B) (msec)	BASELINE	20	443.8 (54.91)	325 - 595			
	DAY 1	17	446.5 (43.82)	368 - 535	17	-6.1 (29.02)	-60 - 60
QRS (msec)	BASELINE	31	108.4 (38.23)	76 - 246			
	DAY 1	29	105.9 (33.21)	76 - 244	29	-2.6 (15.14)	-74 - 10
PR (msec)	BASELINE	27	144.6 (53.73)	0 - 240			
	DAY 1	25	156.4 (47.13)	0 - 248	24	7.5 (42.06)	-32 - 198.8
RR (msec)	BASELINE	27	837.0 (212.89)	200 - 1200			
	DAY 1	24	846.7 (137.29)	604 - 1176	24	14.7 (164.89)	-280 - 500

Note: 1. Baseline for the calculation of change is the latest time point prior to right heart catheterization.
2. QTc(B) is Bazett's QTc interval.

Source: M:\CLINICAL\BDM\Definity\416\Programs\Tables\t-14-3-5-3a-ecg-shift.sas

Reviewer's comment: These ECGs do not capture Tmax.

GE 191-004: This was a single-blind, cross-over, placebo-controlled clinical study of Optison and 5% dextrose (control) study of 30 patients, 11 with normal pulmonary pressures and 19 with pulmonary hypertension, who underwent a resting echocardiogram with Optison along with pulmonary arterial catheterization. In study GE 191-004, each patient underwent two resting echocardiograms, one with Optison and one with dextrose. The order of these two echocardiograms was randomized. 12-lead ECGs were obtained at screening, prior to any echocardiogram, and at discharge. It should be noted that the discharge ECGs were obtained after both echocardiograms. Multiple intervals were measured (PR, RR, QRS, QT, QTcB,

QTcF). These ECGs were centrally read by a core lab. The sponsor summarized these changes, but concludes that no clinically significant changes were observed.

Protocol GE-191-004
A Phase 4, Placebo Controlled, Single-blind, Cross-over Safety Study to Evaluate the Effect of Optison on Pulmonary Artery Systolic Pressure and Pulmonary Vascular Resistance as Measured by Right Heart Catheterization

Table 14.3.14 Summary of Observed and Change from Baseline 12-Lead ECG Data by Treatment Arm and Stratum, Safety Population

Parameter	Visit	Arm A (Optison/Control)			Arm B (Control/Optison)			Overall			
		Statistics	Normal PASP (N=6)	Elevated PASP (N=9)	Overall (N=15)	Normal PASP (N=5)	Elevated PASP (N=10)	Overall (N=15)	Normal PASP (N=11)	Elevated PASP (N=19)	Overall (N=30)
Mean QTcF (msec)	Baseline	n	6	9	15	4	10	14	10	19	29
		Mean	431.2	447.7	441.1	432.8	422.0	425.1	431.8	434.2	433.3
	SD	40.03	28.53	33.27	33.18	23.77	25.90	35.46	28.59	30.51	
	Median	427.0	448.0	446.0	418.5	417.5	417.5	418.5	431.0	423.0	
	Min	385	392	385	412	393	393	385	392	385	
	Max	479	489	489	482	465	482	482	489	489	
	Pre-Discharge	n	5	9	14	4	10	14	9	19	28
		Mean	430.2	453.3	445.1	418.3	426.0	423.8	424.9	438.9	434.4
		SD	52.16	29.83	38.95	18.25	23.83	21.98	39.05	29.60	32.87
		Median	411.0	444.0	437.0	419.5	421.5	421.5	416.0	439.0	429.0
		Min	391	425	391	395	398	395	391	398	391
		Max	520	517	520	439	464	464	520	517	520
	Change	n	5	9	14	4	10	14	9	19	28
		Mean	7.2	5.7	6.2	-14.5	4.0	-1.3	-2.4	4.8	2.5
		SD	21.00	19.56	19.28	33.03	13.44	21.26	27.58	16.16	20.28
		Median	3.0	3.0	3.0	-7.5	2.5	2.5	3.0	3.0	3.0
		Min	-17	-20	-20	-59	-11	-59	-59	-20	-59
		Max	41	37	41	16	28	28	41	37	41

Note 1: Baseline is screening or the latest evaluation prior to the first injection.
Note 2: QTcB=Bazett's Correction, QTcF=Fridericia's Correction.

T14_3_14_EG.SAS/13DEC2010:10:58/PAGE 7 OF 7

Before discharge, 2 subjects in the Optison control arm had an absolute QTcF interval > 500 ms:

- Subject 031104 had a baseline QTcF was 479 ms. This subject had a history of first-degree atrioventricular (AV) block, right axis deviation, and nonspecific intraventricular delay and the pre-discharge QTcF of 520 ms was considered to be due to the left bundle branch block.
- Subject 04/205 had a baseline QTcF of 489 ms; this subject had a history of AV block and the pre-discharge QTcF of 517 ms was considered to be due to the AV block.

Reviewer's comment: Again, these ECGs do not capture T_{max}. It is possible that the change in QTc observed pre-discharge was due to hysteresis following an increase in heart rate with the injection. In addition the ECG was post-procedure and not between injections.

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

/s/

SUCHITRA M BALAKRISHNAN
05/16/2011

NORMAN L STOCKBRIDGE
05/17/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 21-064 BLA#	NDA Supplement #:S- 011 BLA STN #	Efficacy Supplement Type SE- 1
Proprietary Name: Definity® Established/Proper Name: Perflutren Lipid Microsphere Dosage Form: Injectable Suspension Strengths: 10µL/Kg		
Applicant: Lantheus Medical Imaging Agent for Applicant (if applicable): N/A		
Date of Application: September 29, 2010 Date of Receipt: September 29, 2010 Date clock started after UN:		
PDUFA Goal Date: July 29, 2011	Action Goal Date (if different):	
Filing Date: November 29, 2010	Date of Filing Meeting: November 18, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1S		
Proposed indication(s)/Proposed change(s): Indication: For use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of left ventricular endocardial border (b) (4).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov/9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>				
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		X		
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>		X		
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			X	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			X	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			PMHS consult will be sent by 12/20/2010
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):			X	
<i>If yes, distribute minutes before filing meeting</i> Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): August 3, 2009	X			

<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):			X	
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 18, 2010

BLA/NDA/Supp #: 21-064/S-011

PROPRIETARY NAME: Definity®

ESTABLISHED/PROPER NAME: Perflutren Lipid Microsphere

DOSAGE FORM/STRENGTH: 10µL/Kg

APPLICANT: Lantheus Medical Imaging

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: On August 3, 2009 a face to face meeting was held between FDA and Lantheus Medical Imaging Inc. The sponsor wanted to gain agreement with the FDA on their proposed submission strategy which would include (b) (4)

(b) (4)

On September 29, 2010 the sponsor submitted a (b) (4)

The sponsor also proposes revisions to the Boxed Warning, Warnings, Adverse Reactions, (b) (4) sections of the current DEFINITY Package Insert. Data in the submission include post marketing studies.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Frank Lutterodt	Y
	CPMS/TL:	Kyong Kang	Y
Cross-Discipline Team Leader (CDTL)	Libero Marzella		Y
Clinical	Reviewer:	Ross Filice	Y
	TL:	Libero Marzella	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Microbiology (<i>for antimicrobial products)</i>	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Christy John	N
	TL:	Young Moon Choi	Y
Biostatistics	Reviewer:	Janelle Charles	Y
	TL:	LaRee Tracy	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Adebayo Lanionu	N
	TL:	Adebayo Lanionu	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	David Place	N
	TL:	James Vidra	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Bryan Riley	N
	TL:	James McVey	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers Michele Fedowitz	Clinical		Y
Other attendees Charles Ganley			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> 	<input checked="" type="checkbox"/> YES Date if known: May 2, 2010 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: The original data definition files lacked in detail and description pertaining to several categorical variables provided in the primary efficacy and safety data sets. The Agency requested that the sponsor submit detailed data definition files including all codes or definitions for the categorical variables included in all study datasets contained in the submission. In addition, there were several variables in</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>the data sets provided that contained a number of blank entries. The Agency also requested that the sponsor specify the codes or symbols used for missing values in the data definition files. Upon request, the sponsor promptly provided updated and well populated data definition files.</p>	
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Rafel Dwaine Rieves</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

FRANK A LUTTERODT
12/14/2010

KYONG A KANG
12/15/2010