

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021064Orig1s011

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-064

SUPPL # 011

HFD # 160

Trade Name Definity

Generic Name Perflutren Lipid Microsphere

Applicant Name Lantheus Medical Imaging Inc.

Approval Date, If Known 07/31/2001

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2) SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Label revisions related to the safety supplement are:

- Updating the Boxed Warning removing monitoring and/or observation of patients
- Removal of the cautionary statement in the Indications section

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

- Summary of the post approval commitment studies (CARES Registry study and Pulmonary Hypertension study) in the Post-Marketing section

- Proposed updates in (b) (4)

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than

deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-064, the same NDA
for which this efficacy
supplement
is submitted to.

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new

clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

The sponsor conducted a propensity score matching analysis of post marketing clinical data which is essential to the approval. The sponsor also conducted a hemodynamic study and a clinical study of the drug "as used" in medical practice. Together, all 3 were essential for approval and all 3 have not been relied on to support the safety or efficacy of a previously approved drug.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

The sponsor conducted a propensity score matching analysis of post marketing clinical data which is essential to the approval. The sponsor also conducted a hemodynamic study and a clinical study of the drug "as used" in medical practice. Together, all 3 were essential for approval and all 3 have not been relied on to support the safety or efficacy of a previously approved drug

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Title: Regulatory Project Manager
Date: October 21, 2011

Name of Office/Division Director signing form: Rafel Dwaine Rieves
Title: Division Director, Division of Medical Imaging Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

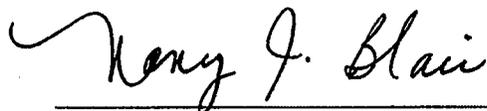
/s/

FRANK A LUTTERODT
10/24/2011

RAFEL D RIEVES
10/24/2011

1.3.3 DEBARMENT CERTIFICATION

Lantheus Medical Imaging, Inc. (Lantheus MI) 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





Signature:

Date:

Nancy J. Blair

Director, Regulatory Affairs

Lantheus Medical Imaging, Inc.

331 Treble Cove Road

North Billerica, MA 01862

2nd cycle (Review)

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21-064 Supplement Number: 11 NDA Supplement Type (e.g. SE5): SE-08

Division Name: Division of Medical Imaging Products PDUFA Goal Date: October 24, 2011 Stamp Date: 8/24/2011

Proprietary Name: Definity

Established/Generic Name: Perflutren Lipid Microsphere

Dosage Form: Injection

Applicant/Sponsor: Lantheus Medical Imaging Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) Activated definity Injectable Suspension is indicated for use inpatients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The safety and efficacy of Definity with exercise stress or pharmacologic stress testing have not been established.

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): _____
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Activated definity Injectable Suspension is indicated for use inpatients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):

* Not feasible:

 Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

 Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

 Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

) Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Additional pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

1st Review Cycle

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21-064 Supplement Number: 11 NDA Supplement Type (e.g. SE5): SE-08

Division Name: Division of Medical Imaging Products PDUFA Goal Date: July 29, 2011 Stamp Date: 9/29/2010

Proprietary Name: Definity

Established/Generic Name: Perflutren Lipid Microsphere

Dosage Form: Injection

Applicant/Sponsor: Lantheus Medical Imaging Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) Activated definity Injectable Suspension is indicated for use inpatients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The safety and efficacy of Definity with exercise stress or pharmacologic stress testing have not been established.

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): _____
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Activated definity Injectable Suspension is indicated for use inpatients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

justification):

* Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

} Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Additional pediatric subpopulation(s) in which studies have been completed (check below):

Population	minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population	minimum	maximum
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 21-064 BLA #	NDA Supplement # 11 BLA STN #	If NDA, Efficacy Supplement Type: SE-08
Proprietary Name: Definity Established/Proper Name: Perflutren Lipid Microspheres Dosage Form: Parenteral		Applicant: Lantheus Medical Imaging Agent for Applicant (if applicable): N/A
RPM: Frank Lutterodt		Division: Division of Medical Imaging Products
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Definity NDA 21-064, the same NDA for which this efficacy supplement is submitted to.</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>The reference listed drug is the same product</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>October 24, 2011</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR 7/29/11

¹ The Application Information section is (only) a checklist. The Contents of Action Package section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) October 24, 2011-Approval July 29, 2011-CR
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	YES
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	YES
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NO

³ Fill in blanks with dates of reviews, letters, etc.

<p>Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<p>❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</p>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	
<p>❖ Proprietary Name</p> <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	
<p>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</p>	<input type="checkbox"/> RPM <input type="checkbox"/> DMEPA <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 6/13/11 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews MHT- 6/28/11 PHT-6/10/11 Labeling Meetings, May 10, 17 and June 6, 2011
Administrative / Regulatory Documents	
<p>❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</p> <p>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</p> <p>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</p>	<p>Statistics November 29 2010 Clin Pharm-December 1, 2010 Clinical-December 3, 2010 Project Manager--December 15, 2010</p> <input type="checkbox"/> Not a (b)(2) July 19, 2011 <input type="checkbox"/> Not a (b)(2) October 21, 2011
<p>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</p>	<input checked="" type="checkbox"/> Included
<p>❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</p>	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>This application does not trigger PREA</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg August 3, 2009
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	May 2, 2011
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/21/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/28/11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	10/21/11 and 7/28/11
• Clinical review(s) (<i>indicate date for each review</i>)	10/24/11 and 7/22/11
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Medical Officer's Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None DCRP-5/17/11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/30/11
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/30/11
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input type="checkbox"/> None
Nonclinical <input checked="" type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input type="checkbox"/> None requested

Product Quality		<input checked="" type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None
❖ Microbiology Reviews		<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) Or 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.
- (3) Or 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) **And** 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.
- (3) **And** 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) Or 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.
- (3) Or 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 ODE's ADRA.

MEMORANDUM OF TELECONFERENCE

MEETING DATE: October 17, 2011
TIME: 2:40PM
LOCATION: Teleconference
APPLICATION: NDA 21-064, S/11
DRUG NAME: Definity (Perflutren Lipid Microspheres)
TYPE OF MEETING: Informal Teleconference

FDA ATTENDEES:

Charles Ganley, M.D., Director, ODEIV
Shaw T. Chen, M.D., Deputy Director, ODEIV
Rafel Dwaine Rieves, M.D., Director, DMIP
Libero Marzella, M.D., Ph.D., Deputy Director, DMIP
Alexander Gorovets, M.D., Clinical Team Leader, DMIP
Lucie Yang, M.D., Ph.D., Acting Clinical Team Leader, DMIP
Dave Roeder, M.S., Associate Director for Regulatory Affairs, OND/OAP
Michael Jones, Rph. Senior Program Management Officer, Office of Regulatory Policy
Kyong Kang, Pharm.D., Chief, Project Management Staff, DMIP
Frank Lutterodt, M.S., Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Nancy Blair, Director, Regulatory Affairs
Michael Duffy, Vice President and General Counsel
William Regan, Regulatory Affairs Consultant
Dana Washburn, M.D., Vice President, Chief Medical Officer

Background:

On September 29, 2011, Lantheus submitted a supplement to their approved application (b) (4) to revise safety information to the label (change the language in current warnings), (b) (4) . (b) (4) multiple sources of information were submitted to support the safety information (published reports, registry study report, observational study report, pulmonary hemodynamics study report,) (b) (4)

It became clear to FDA after review completion that the changes being made to the labeling should have been submitted in 3 separate supplements and a total of three user fees. Because only one fee was paid when the application was submitted in 2010, two additional user fees are necessary if all of the changes to the labeling were to be reviewed. A teleconference was held between the sponsor and FDA to clarify the issue and discuss the path forward for the application.

FDA informed the sponsor that the supplement will be divided into 3 separate supplements as follows:

1. [REDACTED] (b) (4)
2. Safety changes
3. [REDACTED] (b) (4)

The sponsor was offered the following options:

- Pay for all three supplements
- Pay for just one supplement and FDA will issue two “unacceptable for filing” letters
- Pay for two supplements and be issued one “unacceptable for filing” letters

The sponsor stated that they needed to regroup to decide how to proceed.

Drafted by: Frank Lutterodt.

Reviewed by: All FDA attendees.

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/s/

FRANK A LUTTERODT
10/19/2011



NDA 21-064/S-11

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Dear Ms. Blair:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Definity (Perflutren) 10UL/KG IV.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

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

Sincerely,

{ See appended electronic signature page }

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

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/s/

KYONG A KANG
10/12/2011
Signing for Rafael Rieves



NDA 21-064/S-11

INFORMATION REQUEST

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

Dear Ms. Blair:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DEFINITY® Vial for (Perflutren Lipid Microsphere) Injectable Suspension.

We have reviewed your most recent labeling proposal submitted to Supplement-11 of NDA 21064 on 8/24/2011. We agree with some of your proposed labeling changes, but disagree with others. Please find a summary of our thoughts on your proposed changes below. Also, find enclosed a copy of our most recent labeling proposal along with a copy highlighting differences when compared to your most recent proposal.

Numbering

The numbering of the sections of the labels must comply with the specifications in 21 CFR 201.57. Even though removal of sections 8.2 (Labor and Delivery), and 9 (Drug Abuse and Dependence) result in non-consecutive numbering, the other sections must still retain the specified number to ensure consistency between labels. We re-numbered the sections as such.

Boxed Warning

We agree that observation for all patients may be excessively burdensome. We propose removing the second bullet point regarding observation entirely and adding timing information in the first paragraph of the boxed warning.

Dosing and Administration

The abbreviation “mL” was changed to “microL” in your most recent labeling submission. It appears this is an error, so these have been changed back to “mL” unless you disagree.

Warnings and Precautions

- We agree with your proposed wording regarding the risk of reactions in patients with unstable cardiopulmonary conditions
- We agree to add the adverse reaction “bradycardia”
- We agree to remove the adverse reaction “coronary artery occlusion”
- We agree with replacing the symbol “μ” with the word “micro” for clarity

Adverse Reactions

Postmarketing Experience

- [REDACTED] (b) (4)
We believe this statement, stating that death or serious adverse reactions are unlikely to occur at a rate of more than 0.3%, is important to help understand the strengths and limitations of this study.
- [REDACTED] (b) (4)
- We agree with your proposed wording regarding the risk of reactions in patients with unstable cardiopulmonary conditions
- We propose changing the word “symptoms” to “reactions” to be more consistent with other sections
- We agree to add the adverse reaction “bradycardia”
- We agree to remove the adverse reaction “coronary artery occlusion”

Use in Specific Populations

- We propose changing the word “SPECIFICS” to “SPECIFIC” in the heading.
- Numbering has been changed as described above.

Pediatric Use

[REDACTED] (b) (4)

Clinical Pharmacology

- We agree with your proposal to include the statements regarding patients with COPD and patients with hepatic diseases or congestive heart failure. We believe these statements would be more appropriately placed in a new section 12.2.4, Special Populations.

- [REDACTED] (b) (4)

Clinical Studies

Endocardial Border Length

We agree with adding the word “of”

Pulmonary Hemodynamic Effects

We agree with changing “<=” to “≤”

How Supplied/Storage and Handling

Storage and Handling

We agree with including additional information regarding bacterial contamination.

Patient Counseling Information

We propose removing the subheading “17.1” as there is only one section of information.

We request a prompt written response in order to continue our evaluation of your supplemental application.

If you have questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:

Labeling Draft

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

FRANK A LUTTERODT

09/26/2011

From: Lutterodt, Frank A

Sent: Friday, September 23, 2011 12:33 PM

To: 'Blair, Nancy'

Subject: RE: Definity letter

MEMORANDUM OF TELECONFERENCE

MEETING DATE: July 11, 2011
TIME: 9:00 AM
LOCATION: Teleconference
APPLICATION: NDA 21-064 S-11
DRUG NAME: Definity (Perflutren Lipid Microspheres)
TYPE OF MEETING: Review Update

MEETING CHAIR: Dwaine Rieves

MEETING RECORDER: Frank Lutterodt

FDA ATTENDEES:

Dwaine Rieves, M.D., Division Director
Louis Marzella, M.D., Ph.D., Deputy Division Director
Ira Krefting, M.D, Safety Team Leader
Kyong Kang, Pharm.D., Chief, Project Management Staff
Alexander Gorovets, M.D, Clinical Team Leader (via teleconference)
Ross Filice, M.D., Clinical Reviewer
LaRee Tracy, Ph.D., Statistics Team Leader
Janelle Charles, Ph.D., Statistics Reviewer
Gene Williams, Ph.D., Clinical Pharmacology Team Leader
Frank Lutterodt, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES (Lantheus Medical Imaging):

Nancy Blair, Director, Regulatory Affairs
Vannary Sok, Regulatory Affairs Assistant
Stephen Schmitz, M.D., Medical Director, Pharmacovigilance
Gajanan Bhat, Ph.D., Director of Biostatistics and Data Management
Mark Hibberd, M.D., Senior Medical Director, Medical Affairs
Mary Taylor, MPH. Vice President, Regulatory Affairs and Quality
Dana Washburn, M.D., Vice President Clinical Development & Medical Affairs

AGENDA:

NDA 21064 (Definity), supplement dated September 29, 2010, the Division requested a teleconference to provide review update to the applicant.

DISCUSSION POINTS:

FDA informed the applicant that a consensus could not be reached on the labeling due to deficiencies in the data and hence the labeling cannot be developed [REDACTED] (b) (4)

The applicant stated their belief that the process was agreed upon during a meeting with the agency prior to filing the Supplemental New Drug Application.

(b) (4)

The applicant was encouraged to consider prospective, adequate, and well-controlled clinical trials to support efficacy claims. FDA told the applicant that details of concerns are being developed and will be open to further discussions after concerns are conveyed in writing to the applicant.

The applicant expressed concern that the proposed text in the boxed warning (b) (4) _____ represented a significant change from currently approved labeling. FDA stated that perhaps a consensus could be reached on the wording.

The applicant expressed the desire for a face-to-face meeting in the future to discuss the path forward. FDA agreed to provide the opportunity to meet.

ACTION ITEMS:

FDA will forward written concerns to the applicant by the PDUFA due date.

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/s/

FRANK A LUTTERODT
07/17/2011

From: Lutterodt, Frank A
Sent: Thursday, July 14, 2011 2:20 PM
To: 'Blair, Nancy'
Subject: Minutes for June 11th TCON

MEMORANDUM OF TELECONFERENCE

MEETING DATE: June 27, 2011
TIME: 10:00 AM
LOCATION: Teleconference
APPLICATION: NDA 21-064 S-11
DRUG NAME: Definity (Perflutren Lipid Microspheres)
TYPE OF MEETING: Labeling Discussion

MEETING CHAIR: Dwaine Rieves/ Ross Filice

MEETING RECORDER: Frank Lutterodt

FDA ATTENDEES:

Dwaine Rieves, M.D., Division Director
Ira Krefting, M.D, Safety Team Leader
Ross Filice, M.D., Clinical Reviewer
LaRee Tracy, Ph.D., Statistics Team Leader
Janelle Charles, Ph.D., Statistics Reviewer
Christy John, Ph.D., Clinical Pharmacology Reviewer
Gene Williams, Ph.D., Clinical Pharmacology Team Leader
Renee Tyson, M.A., Senior Regulatory/Safety Project Manager
Frank Lutterodt, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Nancy Blair, Director, Regulatory Affairs
Vannary Sok, Regulatory Affairs Assistant
Shama Alam, M.D. Associate Director, Pharmacovigilance
Gajanan Bhat, Ph.D., Director of Biostatistics and Data Management
Mark Hibberd, M.D., Senior Medical Director, Medical Affairs
Mary Taylor, MPH. Vice President, Regulatory Affairs and Quality
Dana Washburn, M.D., Vice President Clinical Development & Medical Affairs

AGENDA:

NDA 21064 (Definity), supplement dated September 29, 2010, the Division requested a teleconference to convey labeling information to the applicant.

DISCUSSION POINTS:

FDA discussed highlights of key changes on the labeling originally proposed by the applicant in the September 29, 2010 sNDA submission. The following changes were pointed out to the sponsor:

- 1) Boxed warning has been maintained, but will modify the monitoring requirements and convey our best understanding of the incidence of severe reactions.
- 2) Indication statement has been modified to remove statement regarding stress testing.
- 3) [REDACTED] (b) (4)
- 4) Results from two postmarketing studies have been included; the prospective safety registry and the pulmonary hemodynamic study. The retrospective observational database review was not included because of methodological concerns expressed by the statistical team and at the recent Advisory Committee meeting.
- 5) [REDACTED] (b) (4)

ACTION ITEMS:

FDA will forward draft labeling to the applicant in short order.
FDA is open to further discussions with the applicant following their review of proposed labeling.

ATTACHMENTS/HANDOUTS:

Draft Labeling

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

FRANK A LUTTERODT
07/05/2011

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)

TYPE C NDA TELECONFERENCE MINUTES

NDA: 21064
DRUG NAME: Definity
SPONSOR: Lantheus Medical Imaging
DATE: Thursday, June 9, 2011 at 11:00 am, EDT
DIAL-IN #: (866) 842-8970 (temporary)

SPONSOR PARTICIPANTS

Nancy Blair, Director, Regulatory Affairs
Gajanan Bhat Ph.D., Director, Data Management and Biostatistics

FDA PARTICIPANTS

Ross Filice, M.D., Clinical Reviewer
Ira Krefting, M.D, Safety Team Leader
Lou Marzella, M.D., Deputy Division Director
Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager
Dwayne Rieves, M.D., Division Director

AGENDA: NDA 21064 (Definity), supplement dated September 29, 2010, the Sponsor would like clarification to the FDA Clinical Information Request (IR) of June 6, 2011 (see Attachment), regarding the Geriatric Use section of the labeling.

With regards to the FDA Clinical Information Request, June 6, 2011, specifically to address the Geriatric Use section of the labeling, the Sponsor states they are unable to provide summary data regarding patients between 65-74 years of age and greater than 74 years of age. This is because the clinical trials used to support the original application date to the 1990s, at the time only data for those patients greater than or equal to 65 years of age was required, and they do not have these source data readily available.

As the drug has been on the market for a relatively long period of time, we do not feel that adding data for patients greater than 74 years of age will provide additional valuable information for prescribers. The Sponsor agreed to provide summary data from the original clinical trials for patients less than 65 years of age and greater than or equal to 65 years of age, by June 17, 2011.

Minutes Recorded By: T.Nguyen, DMIP

From: Lutterodt, Frank A
Sent: Monday, June 06, 2011 1:57 PM
To: 'Blair, Nancy'
Subject: Information Request for Definity sNDA

DIVISION OF MEDICAL IMAGING PRODUCTS

INFORMATION REQUEST TO THE APPLICANT

Lantheus Medical Imaging
Attention: Nancy J. Blair
Associate Director, Regulatory Affairs
Definity® Vial for (Perflutren Lipid Microsphere) Injectable Suspension
NDA 21-064/ S-011

Dear Nancy: Please find information request for Definity attached below: Thank you

Our review of your supplemental application to NDA 21064 submitted on September 29, 2010 is ongoing. We have the following information request:

1. The specific labeling requirements for the Geriatric Use section of labeling in the case where studies have demonstrated that no differences in safety or effectiveness have been observed [21 CFR 201.57(c)(9)(v)(B)(2)] are as follows:

If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection must contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), __ percent were 65 and over, while __ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Therefore, in order to use the required language in the second paragraph above, we request you provide the following summary data:

- a. Total number and percent of patients who were:

- i. <65 years old
- ii. 65-74 years old
- iii. ≥ 75 years old

with totals reported in the following groups:

- a. All patients
- b. Patients in rest echocardiography
- c. Patients in stress echocardiography

from the following data sources:

- a. Clinical trials from your original submission that support the conclusion that adverse event rates are similar in these groups.
- b. Clinical trials from the current submission which continue to support the conclusion that adverse event rates are similar in these groups.

Please respond by Friday, June 17, 2011.

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/s/

FRANK A LUTTERODT
06/06/2011

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/s/

THUY M NGUYEN
06/09/2011

From: Lutterodt, Frank A
Sent: Wednesday, May 11, 2011 3:47 PM
To: 'Blair, Nancy'
Subject: Stats Information Request for DMP 501.doc

COMMENTS TO THE SPONSOR

Lantheus Medical Imaging
Attention: Nancy J. Blair
Associate Director, Regulatory Affairs
Definity® Vial for (Perflutren Lipid Microsphere) Injectable Suspension
NDA 21-064

Dear Nancy: Find attached information request for (b) (4) attached.

Thank you,

Frank

COMMENTS TO THE SPONSOR



Please provide response to this information request within seven business days.

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/s/

FRANK A LUTTERODT
05/13/2011

From: Lutterodt, Frank A
Sent: Friday, April 08, 2011 2:25 PM
To: Taylor, Mary
Cc: 'Blair, Nancy'
Subject: Clinical IR.doc

Dear Ms. Taylor, Nancy is probably still out of the office so I am forwarding yet another information request(attached) to your attention.

Thank you,
Frank
Frank

April 8, 2011

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

RESPONSES TO THE SPONSOR

Lantheus Medical Imaging

Attention: Nancy J. Blair

Associate Director, Regulatory Affairs

Definity® Vial for (Perflutren Lipid Microsphere) Injectable Suspension

NDA 21-064

With reference to the Definity Periodic Safety Update Report 11 (time period 28 December 2009 to 27 December 2010), we note that Lantheus has identified the following cases:

1. 768 cases (cumulative) in a search using MedDRA (version 13.0) SMQ "anaphylaxis"
2. 64 cases in a separate query for "hypersensitivity" (described in section 9.1.2 "Anaphylactic/anaphylactoid reactions including hypersensitivity reactions")
3. 25 cases in a query using SMQ "convulsions" (described in section 9.1.3)
4. 97 cases in a query using SMQ "shock" (described in section 9.1.4)

Please clarify whether these cumulative counts of cases include other duplicates, or potential duplicates have been removed.

We note that line listings with information for these cases are included in Appendix 8. We request an additional listing of these cumulative cases in a spreadsheet (e.g., Excel) with the following information in each row:

1. case reference number
2. country of origin

3. patient age
4. patient sex
5. manufacturer initial receipt date
6. event date (if available)
7. serious criteria, including fatal, life-threatening, requires hospitalization, etc.
8. coded reactions (MedDRA preferred terms)

We also request that you send us a copy of the Data Monitoring Committee report for the DMC meeting scheduled for April, 2011, if available.

Please respond by Friday, April 15, 2011.

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/s/

FRANK A LUTTERODT
04/11/2011

From: Lutterodt, Frank A
Sent: Thursday, April 07, 2011 5:37 PM
To: 'Blair, Nancy'
Cc: Taylor, Mary
Subject: Statistical Information Request for Definity Postmarketing study 418

Hello Ms. Taylor, Please find attached information request for Definity. Thank you.

April 7, 2011

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

RESPONSES TO THE SPONSOR

Lantheus Medical Imaging

Attention: Nancy J. Blair

Associate Director, Regulatory Affairs

Definity® Vial for (Perflutren Lipid Microsphere) Injectable Suspension

NDA 21-064

This information request is in reference to the postmarketing study DEFINITY-418 titled 'A Retrospective Observational Database Study to Compare In-Hospital All-Cause Mortality in Critically Ill Patients Undergoing Echocardiography With or Without Definity' submitted under NDA 21064.

1. Please provide the number of patients who underwent echocardiography with Definity or non-contrast by calendar year during the study period.
2. Please provide the number and percentage of patients who died during 24 hours following echocardiography by treatment (Definity or non-contrast) and calendar year during the study period. Also, provide these summaries for patients who died 48 hours following echocardiography.

Below is a suggested table for providing these summaries, however, you may organize information as appropriate.

Year	24 Hour Mortality						48 Hour Mortality					
	Definity			Non-contrast			Definity			Non-contrast		
	N	n	%	N	n	%	N	n	%	N	n	%
2002												
2003												
2004												
2005												
2006												
2007												
2008												

*In this table, N is number of patients undergoing echocardiography with Definity or non-contrast for the specified calendar year, n is the number of 24 hour or 48 hour deaths during that year and % the corresponding percentage of deaths.

Please provide your response to this information request within 10 business days.

Thank you,

Frank Lutterodt

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/s/

FRANK A LUTTERODT
04/11/2011

A complicating factor is that the label specifies that this agent should only be used in those patients with suboptimal (aka obese) patients. (b) (4)

[Redacted text block]

From: Lutterodt, Frank A
Sent: Tuesday, February 15, 2011 2:45 PM
To: 'Blair, Nancy'
Subject: Information Request Feb 15 2011.doc

Dear Nancy: Please find below information Request for Definity sNDA 21-064/S-011. Response is due by Thursday, February 24, 2011. Call me if you have any questions.

Regards,
Frank

February 15, 2011

DIVISION OF MEDICAL IMAGING PRODUCTS

INFORMATION REQUEST TO THE APPLICANT

Lantheus Medical Imaging
Attention: Nancy J. Blair
Associate Director, Regulatory Affairs
Definity® Vial for (Perflutren Lipid Microsphere) Injectable Suspension
NDA 21-064/ S-011

Our review of your submissions dated 9/29/2010, 11/22/2010, 12/16/2010, and 2/14/2011 for supplementary New Drug Application 21064 are ongoing. We have the following additional information requests regarding protocol (b) (4)



Please respond by Thursday, February 24, 2011.

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/s/

FRANK A LUTTERODT
02/15/2011

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 20, 2010
TIME: 9:30 AM
LOCATION: Teleconference
APPLICATION: NDA 21-064
DRUG NAME: Definity®

MEETING RECORDER: Frank Lutterodt

FDA ATTENDEES:

Rafel Dwaine Rieves, M.D., Division Director, DMIP
Liberio Marzella, M.D., Deputy Division Director, DMIP
Ross Filice, M.D., Clinical Reviewer, DMIP
Lucie Yang, M.D., Clinical Reviewer, DMIP
Frank Lutterodt, M.S., Regulatory Project Manager

SPONSOR ATTENDEES:

Nancy J. Blair, Associate Director, Regulatory Affairs
Mary Taylor, Vice President, Global Regulatory Affairs

TELECONFERENCE

The Division of Medical Imaging Products requested a brief teleconference with Lantheus Medical Imaging to inform them that, a follow-up Advisory Committee (AC) discussion of ultrasound contrast agent safety is being tentatively scheduled for May 2, 2011.

The sponsor was informed that, the purpose of AC meeting is to provide updates on safety information and post-marketing requirements for ultrasound contrast agents. Hence, it will be a follow-up to the AC meeting in 2008 and the Committees involved would be: Cardiovascular and Renal, Drug Safety and Risk Management, as well as other imagers and echocardiographers.

The sponsor was also informed that, participants would be the same as 2008 (GE Healthcare, Lantheus Medical Imaging and Bracco).

DECISIONS (AGREEMENTS) REACHED:

The sponsor agreed to communicate with the Division between now and the AC date to have an understanding of each other's position and assessment of data. The sponsor also agreed on tentative dates below:

- Prepare a briefing package for the ACS (due 3/31/11)
- Prepare slides for a brief presentation (due 4/28/11)

ACTION ITEMS:

The Division will keep the sponsor abreast with plans for the AC.

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/s/

FRANK A LUTTERODT
12/21/2010



NDA 21-064/S-011

FILING COMMUNICATION

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

Dear Ms. Blair:

Please refer to your New Drug Application (NDA) dated September 29, 2010, received September 29, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for DEFINITY® Vial for (Perflutren Lipid Microsphere) Injectable Suspension.

We also refer to your submission dated November 23, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 29, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team, and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 17, 2011.

During our filing review of your application, we identified the following potential review issues:



(b) (4)

2. Subgroup analysis by age, gender, and race is required for efficacy and safety data [21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a)]. This has already been done for DMP 115-418, but otherwise appears incomplete or absent in the remaining trials. Please provide these analyses along with statistical methods used, or justification for exclusion, for the following trials:

- a. (b) (4)
- b. (b) (4)
- c. (b) (4)
- d. DMP 115-416
- e. DMP 115-415
- f. (b) (4)

and for the following five individual trials from (b) (4):

(b) (4)

3. A signed statement of Good Clinical Practice that states that all clinical studies were performed under the supervision of an IRB and with adequate informed consent procedures is not found in the original submission. Please provide this signed statement or clarification of its location.

4. (b) (4)
deferred pediatric requirements described in the approval letter dated January 22, 2001. Please refer to 21 CFR 314.55 for full details on the required assessments for pediatric use information. We have several questions regarding (b) (4) as follows:

- a. (b) (4)
- b. The approval letter from 2001 suggested performing pediatric studies in patients greater than 2 years of age along with preclinical studies in immature lung animal models prior to neonatal studies because of potential risk to younger patients.

(b) (4) Please comment.

- c. (b) (4)

(b) (4)

5. Further clarification is also requested regarding the results of study (b) (4) as follows:
- a. Regarding the patients who did experience transient vital sign changes, how many patients were affected?
 - b. Provide a per patient summary of all subjects who experienced vital sign changes.
 - i. Is this subset of patients exclusively similar?
 - ii. Did these changes all resolve, i.e. were they all definitely transient?
 - c. The principal investigator (PI) determined that none of the changes were clinically significant. What was the determination of “clinically significant”? For example, were the changes greater than 10% from baseline, or did the changes persist or not return to baseline?
 - d. How many patients received dobutamine stress?
 - e. How many patients were sedated or under general anesthesia?
 - f. Please provide the criterion for selecting the doses used in the study. For example, were they based on the literature or other sources?

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

ADVISORY COMMITTEE MEETING

We are conceptualizing a follow-up advisory committee discussion of ultrasound contrast agent safety in 2011 and since data from your NDA may prove especially pertinent to our considerations, you will be updated with respect to our plans.

REQUIRED PEDIATRIC ASSESSMENTS

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

[REDACTED] (b) (4)

Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. [REDACTED] (b) (4). If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required. Please see 21 CFR 314.55 for full details.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

RAFEL D RIEVES
12/10/2010

From: Lutterodt, Frank A
Sent: Monday, December 06, 2010 9:34 AM
To: 'Blair, Nancy'
Subject: DEFINITY sNDA 21064 data request 12 03 10.doc

Nancy: Please find IR for your sNDA below. Response is due by December 16, 2010.
Thank you,

Frank

December 6, 2010

DIVISION OF MEDICAL IMAGING PRODUCTS

INFORMATION REQUEST TO THE APPLICANT

Lantheus Medical Imaging

Attention: Nancy J. Blair

Associate Director, Regulatory Affairs

Definity® Vial for (Perflutren Lipid Microsphere) Injectable Suspension

NDA 21-064/ S-011

This is a statistical information request for the SAS codes used by Lantheus Medical Imaging (LMI) in conducting all efficacy analyses as reported in the Clinical Study Report for [REDACTED] ^{(b) (4)}, based on the datasets submitted to NDA 21-064 on September 29 2010. We are also requesting two additional analyses datasets, created from the original datasets (ASDL.XPT, DELINEAT.XPT and BLENGTH.XPT) or raw datasets for submission to the NDA for our ongoing review. We request that the datasets be submitted in SAS transport (.xpt) format. Additionally we request that the SAS codes used to create these datasets also be submitted to NDA 21-064.

The details on the components of these datasets are provided below:

1.

2.

(b) (4)

Please submit the data definition files for the above two requested datasets. The tables below contain possible variable names and codes for the entries in the respective datasets requested. LMI may use the variable names and codes as listed; however, we request that you submit finalized data definition files in .pdf format for each of the datasets created for completeness. Please include in the data definition files any codes used for missing values or entries that are not available/not applicable.





Please respond to this request by December 16, 2010.

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/s/

FRANK A LUTTERODT
12/07/2010

From: Lutterodt, Frank A
Sent: Thursday, November 18, 2010 4:06 PM
To: 'Blair, Nancy'
Cc: Taylor, Mary
Subject: RE: Definity NDA s21-064

Nancy, as discussed in our Phone conversation we have identified the following potential refuse to file issue with your application:

1. The data definition files lack in detail and description pertaining to the several categorical variables provided in the primary efficacy and safety data sets. We request that you 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 are several variables in the provided data sets that contain a number of blank entries. The data definition files should specify the codes or symbols used for missing values.

Please provide initial e-mail response by Tuesday November 23, 2010 followed by a submission to the application by November 29, 2010.

Regards,
Frank

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/s/

FRANK A LUTTERODT
11/22/2010



NDA 21-064/S-011

PRIOR APPROVAL SUPPLEMENT

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

Dear Ms. Blair:

We have received your September 29, 2010, Supplemental New Drug Application (sNDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21-064
SUPPLEMENT NUMBER: 011
PRODUCT NAME: DEFINITY® Vial for (Perflutren Lipid Microsphere)
Injectable Suspension
DATE OF SUBMISSION: September 29, 2010
DATE OF RECEIPT: September 29, 2010

This supplemental application proposes

(b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 28, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at:

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 21-064/S-011**, submitted on September 29, 2010, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT
10/13/2010

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

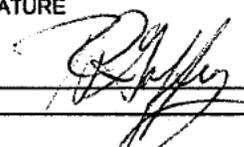
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See the attached listing	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Robert P. Gaffey	TITLE V.P. of Finance and Information Technology
FIRM/ORGANIZATION Lantheus Medical Imaging, Inc.	
SIGNATURE 	DATE (mm/dd/yyyy) 9-15-2010

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850



NDA 21-064

MEETING MINUTES

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

Dear Ms. Blair:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Definity®, Vial for (Perflutren Lipid Microsphere) Injectable Suspension.

We also refer to the meeting between representatives of your firm and the FDA on August 3, 2009. The purpose of the meeting was to discuss your proposed submission strategy [REDACTED] ^{(b) (4)} and to gain agreement with the FDA that sufficient data exist to support a supplemental New Drug Application (sNDA).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C, Meeting
Meeting Category: Pre-NDA

Meeting Date and Time: August 3, 2009
Meeting Location: CDER White Oak Campus

Application Number: NDA 21-064
Product Name: Definity®, Vial for (Perflutren Lipid Microsphere) Injectable Suspension.
Indication: Ultrasound Contrast Agent for Cardiology

Sponsor/Applicant Name: Lantheus Medical Imaging

Meeting Chair: Rafel Dwaine Rieves
Meeting Recorder: Frank Lutterodt

FDA ATTENDEES

Rafel Rieves, M.D.	Division Director
Alex Gorovets, M.D.	Medical Team Leader
Ira Krefting, M.D.	Safety Team Leader
Libero Marzella, M.D., Ph.D.	Medical Team Leader
Michele Fedowitz, M.D.	Medical Officer
Lucie Yang, M.D., Ph.D.	Medical Officer
Jyoti Zalkikar, Ph.D.	Statistics Team Leader
Satish Misra, Ph.D.	Statistics Reviewer
Frank Lutterodt, M.S.	Regulatory Project manager

SPONSOR ATTENDEES

Scott Edwards, Ph.D.	Vice President, Global Research and Regulatory Affairs
Mary Taylor	Vice President, Global Regulatory Affairs
Qi Zhu, M.D.	Senior Medical Director, Global Clinical Research and Development
Mark Hibberd M.D., PhD,	Senior Medical Director, Global Medical Affairs
Steven Schmitz, M.D.	Medical Director, Global Pharmacovigilance, Medical Affairs
Nancy Blair,	Associate Director, Regulatory Affairs
Gajanan Bhat, Ph.D.	Director of Biostatistics and Data Management, Global Clinical Research and Development
Jill Mundy	Director, Definity Marketing
Michael Main, M.D.	Medical Director, Echocardiography Laboratory Saint Luke's Mid-America Heart Institute, Kansas City, MO
Veronica Lee, M.D.,	Medical Director, Global Clinical Research and Development

1.0 BACKGROUND

On May 15, 2009 Lantheus Medical Imaging submitted a meeting request proposing to discuss the submission strategy which would include (b) (4) and to gain agreement with the FDA that sufficient data exist to support a supplemental New Drug Application (sNDA). The FDA granted a Type C meeting which was scheduled for August 3, 2009. Reference is also made to the meeting package from sponsor dated July 2, 2009, received on July 6, 2009. This submission served as the basis for discussions during the August 3, 2009, 2:00 to 3:30 PM, scheduled Face-to Face meeting. The FDA completed review of this submission and provided preliminary responses and comments to the specific questions in the meeting package on July 30, 2009.

2. DISCUSSION

Following introductions between FDA and sponsor representatives, the meeting began with sponsor's slide presentations (attached) in response to FDA's comments dated July 30, 2009.

2.1. Proposed Indication

Sponsor clarified to FDA (b) (4)
(b) (4)

The current Definity indication reads:

*“Activated Definty® (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 left ventricular endocardial border. **The safety and efficacy of Definty® with exercise stress or pharmacologic stress have not been established.**”*

Sponsor's proposed indication would read as follows:

“Activated Definty® (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 left ventricular endocardial border (b) (4)

The FDA stated that the proposal appears reasonable but sufficiency of the data to support the labeling change is a different issue. (b) (4)

2.2 (b) (4)e (Question 4 and 5)

(b) (4)

2.3 Integrated Summary of Safety and Statistical Analysis Plan for Sponsored Studies

FDA asked about the number of well defined protocols involved in the studies that would be supplied within the application. Sponsor stated that most of the studies were performed with well defined Phase 2 and 3 protocols that were submitted at an earlier time to FDA for review.

(b) (4)

. FDA inquired of the types of populations in the studies.

Sponsor agreed to provide integrated summary of safety and a statistical analysis plan.

2.4 Sponsor Conducted Efficacy Study

(b) (4)

2.5 Other Discussion

(b) (4)

FDA asked if data on wall motion abnormality (WMA) was collected as it would be useful to show improvement in WMA. Sponsor asked whether a re-read of images to assess segment to segment variability and endocardial border length would be helpful. FDA noted that a re read of the images for endocardial border length could potentially be useful.

2.6 Labeling

FDA suggested that sponsor should refer to guidance regarding the submission of labeling in PLR format as non-PLR labeling format submission could slow down the review process.

2.7 Pediatric Waiver or Plan

FDA encouraged sponsor to submit a pediatric plan or waiver with justification.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

None

The meeting came to a close at 3:15 PM

5.0 ATTACHMENTS AND HANDOUTS

- FDA's responses to sponsor on July 30, 2009.
- Sponsor's slide presentation.

From: Lutterodt, Frank A
Sent: Thursday, July 30, 2009 8:10 AM
To: 'Blair, Nancy'
Subject: NDA 21-064 FDA's Response to Specific Questions in MP

July 30, 2009

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

RESPONSES TO THE SPONSOR

Lantheus Medical Imaging
Attention: Nancy J. Blair
Associate Director, Regulatory Affairs
Definity® Vial for (Perflutren Lipid Microsphere) Injectable Suspension
NDA 21-064

Please refer to your meeting request dated May 15, 2009, received May 18, 2009, requesting a Type C meeting, with the Division of Medical Imaging and Hematology Products (DMIHP) to discuss data results and planned 505(b)(2) Supplemental New Drug Application (sNDA) (b), (4) for Definity (Perflutren Lipid Microsphere) Injectable Suspension.

As noted in the Division's June 3, 2009, "Meeting Granted" letter, based on the submitted statement of purpose, objectives, and proposed agenda, we considered the meeting a Type C meeting as described in our guidance for industry titled "Formal Meetings with Sponsors and Applicants for PDUFA Products".

Reference is also made to the meeting background package dated July 2, 2009. This submission will serve as the basis for discussions during the August 3, 2009, 2:00-3:30 PM, scheduled Face-to-Face meeting. The Division has completed the review of this submission and our preliminary responses and comments to the specific questions in the meeting package are provided below.

These comments should not be considered as an official FDA position. They are meant to promote and facilitate a collaborative and successful exchange during the upcoming Face to Face meeting.

If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting by contacting the Regulatory Project Manager.

For ease of review, your List of Specific Questions (section 2.7) in your Meeting Package has been separated into smaller segments and presented in Italic font followed by the Division's responses in bold font.

Sponsor's Question #1: *LMI believes that [REDACTED] (b) (4)*
[REDACTED]
[REDACTED]
[REDACTED]. *Does the Agency agree?*

FDA Response to Question #1:

- 1. The extent to which usage data and expert opinion verify "clinical acceptance" is open to much interpretation and we decline to offer an opinion on this matter. As you are aware, substantial evidence of safety and efficacy is anticipated to accompany an NDA supplement for a newly proposed indication.**
- 2. Regarding the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) Consensus Statements, if data were available (i.e. the protocol and results of a systematic review of the literature or patient level data from adequately controlled clinical trials), it could potentially be used for exploratory purposes to plan a well-controlled phase 3 study [REDACTED] (b) (4)**
[REDACTED]

Sponsor's Question #2: *The Agency recently accepted that retrospective mortality data from the Premier Perspective™ Database can be used to fulfill a safety commitment study of DEFINITY®. LMI believes that data from the database of [REDACTED] (b) (4)*
[REDACTED]
[REDACTED]
[REDACTED]

FDA Response to Question #2:

- 1. [REDACTED] (b) (4)**

2.

3.



Sponsor's Question #3:

[Redacted] (b) (4)
[Redacted]
[Redacted] Does FDA agree that this approach is sufficient and acceptable to demonstrate the safety of DEFINITY® [Redacted] (b) (4)?

FDA Response to Question #3:

We question the usefulness of this approach [Redacted] (b) (4)

[Redacted]. In the event you wish to explore this possibility, we have the following comments:

1. **Tabular and / or narrative summaries of the published literature or sponsor-conducted studies are not sufficient for review.**

2. **For an examination of the published literature, we would require a pre-specified, systematic review of the literature for comprehensive safety information and an analysis of these data. Any analysis of these data should account for the many variables inherent in the published literature, including:**
 - a. **Limited study design.** It appears that the designs of the submitted narratives are mainly retrospective analyses of data (chart review, patient records, database search). Additionally, in certain studies (b) (4), it is not clear that safety was a pre-specified endpoint.)
 - b. **Variability in study design and study conduct, specifically:**
 - i. **Contrast agents:**
 1. **Type.** It appears that contrast administration not selected out for DEFINITY®, Optison was used in all of the publications.
 2. **Dose and technique of dosing**
 - ii. **Echocardiographic technique (Mechanical Index / Harmonic imaging)**
 - iii. **Population:** It is not clear that contrast was always used in the population of intended use (i.e. patients with sub optimal baseline images) to be consistent with the label.
 - iv. **Outcomes**
 1. **What level of safety monitoring (ECG, BP, AEs, etc.) was employed?**
 2. **What type of “safety” events (death, renal toxicity, and CV events)?**
 3. **What was the quality of these events (duration, severity)**
 - v. **Stress technique (exercise vs. various pharmacologic)**

3. For any sponsor-conducted studies to be relevant for an exploratory analysis of safety, we would require
 - a. Extraction of patient level safety data from the studies, including the level of monitoring obtained in these studies (i.e. parameters such as heart rate, respiratory rate, blood pressure, SaO₂, ECG data, and Adverse Event data)
 - b. Accounting for the variability of safety outcomes including the type, duration and severity of these events
 - c. Accounting for the variability of the studies with respect to
 - i. Dosing and technique of contrast injection
 - ii. Echocardiographic technique (MI/Harmonic)
 - iii. Population (not clear intended population)
 - iv. Stress technique (exercise vs. various pharmacologic)
 - d. Accounting for issues specific to the studies submitted
 - i. . it is not clear that a rigorous plan for collection of safety data was part of all of the studies
 - ii. Inclusion of non-randomized studies (b) (4) which may introduce bias.
 - e. A pre-specified statistical analysis plan for the evaluation of the data.

Sponsor's Question #4.

(b) (4)
Can FDA comment on the data presented and its relevance to a 505(b)(2) submission?

FDA Response to Question #4:

While published literature and original studies may be submitted to support a 505(b)(2) supplemental NDA submission, we question the potential persuasiveness of data from your outlined approach. Additionally, we encourage the conduct of adequate and well controlled phase 3 trials to support safety and efficacy (b) (4)
Should you wish to use the published literature and sponsor-conducted studies for exploratory analysis, we have the following comments regarding the submitted material:

1. **Tabular and / or narrative summaries of the published literature or sponsor-conducted studies are not sufficient for review.**

- 2.

(b) (4)

- a. **Please refer to the FDA Guidance for Industry titled, “Developing Medical Image Drug and Biologic Products, Part 2: Clinical Indications.” This guidance states, that the labeled indications for medical imaging agents fall within the following general categories: structure delineation; disease or pathology detection or assessment; functional, physiological, or biochemical assessment; and diagnostic or therapeutic patient management.**

- b.

(b) (4)

3. **Removing the statement, “The safety and efficacy of DEFINITY® with exercise stress or pharmacologic stress testing have not been established” would require adequate and well controlled studies..**

- 4.

(b) (4)

(b) (4)

5. **A submission which relies on literature studies will require**

- a. **A detailed, pre-specified systematic review of the literature and pre-specified statistical analysis of the data, that includes clearly stated endpoints, objectives (for example, null and alternative hypotheses), sensitivity analyses and the details of analyses method**

- b. Accounting for and rectification of the variability of the procedure in the published literature with the label, specifically**
 - i. The dosing and administration of the study drug**
 - ii. The use of Harmonic Imaging**
 - iii. The Mechanical Index (MI)**
 - iv. The various stress techniques (exercise vs. various pharmacologic)**
 - v. The patient population (i.e. is there an adequate database to support the population of intended use – patients with suboptimal echocardiograms)**

- c. Accounting for the variability in the study design and conduct including**
 - i. Blinding of image reads**
 - ii. Efficacy outcomes**
 - iii. Appropriateness and uniformity of truth standard**

(b) (4)

The data as presented appear insufficient.

- 6.**
- 7.**
- 8.**
- 9.**
- 10.**



- 11. The variability of the procedure in these studies will need to be rectified with the label, specifically**

- a. The dosing and administration of the study drug
- b. The use of Harmonic Imaging
- c. The Mechanical Index (MI)
- d. The applicability to pharmacologic stress, since only exercise stress was employed.

Sponsor's Question #5:

(b) (4)

[Redacted text block containing the question content]

FDA Response to Question #5:

(b) (4)

[Large redacted text block containing the FDA response content]

3. The Reference Standard will need to be well defined, depending on the primary endpoint. For example,

a.



b.

Sponsor's Question #6: *What type of electronic data sets does the Agency want in this 505(b)(2) supplement?*

FDA Response to Question #6:

Please refer to FDA's Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – General Considerations"

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072362.pdf>

Please refer to FDA's Guidance for Industry "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related FRSubmissions Using the eCTD Specifications"

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

The data sets to be submitted to the Agency should be in xpt format, should have information on all variables listed in section 7.5 of your Statistical Analysis Plan, should have definition file and preferably one record per patient/per study for the meta-analysis part. For the mortality benefit plan, all the data extracted from the Premier Perspective™ Database should be provided in xpt format along with associated definition file. We recommend you to submit, well in advance of the systematic review, a detailed statistical analysis plan that includes clearly stated endpoints, objectives (for example, null and alternative hypotheses), sensitivity analyses (if any) and the details of analyses method, data submission format and definition file. . We recommend you to obtain our comments upon this plan prior to initiation of the systematic review and assessment of mortality benefit review.

Sponsor's Question #7: *Would the Agency prefer to have a pre-sNDA meeting?*

FDA Response to Question #7:

We encourage sponsors to request a Pre-sNDA meeting. However, we question the appropriateness of a meeting at this time given the insufficiency of your proposed database development plan.



**TYPE C MEETING – DEFINITY NDA
21-064**

**Lantheus Medical Imaging Inc.
3 August 2009**



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Clarification of FDA Comments

- **Proposed Indication**

(b) (4)

- **Evidence of Data for 505(b)(2) sNDA**

(b) (4)

- **Analysis of Safety Data**

(b) (4)



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



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Clarification of Responses to Question 4

PROPOSED 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 (b) (4)

- (b) (4)
- **“Removal of statement of safety and efficacy in stress would require adequate and well controlled studies”**

- (b) (4)



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9 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21064	GI 1	LANTHEUS MEDICAL IMAGING INC	DEFINITY (PERFLUTREN) 10UL/KG IV

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
09/02/2009