# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## NDA 21-064/s024

| | |
|---|---|
| ***Trade Name:*** | DEFINITY RT Vial for Injectable Suspension |
| ***Generic or Proper Name:*** | Perflutren Lipid Microsphere |
| ***Sponsor:*** | Lantheus Medical Imaging, Inc. |
| ***Approval Date:*** | November 11, 2020 |
| ***Indication:*** | A contrast agent used for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve delineation of the left ventricular endocardial border. |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# NDA 21-164/s024

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 21-064/s024

# APPROVAL LETTER

NDA 021064/S-024

**SUPPLEMENT APPROVAL**

Lantheus Medical Imaging, Inc.
Attention: Laura Lee
Director, Regulatory Affairs
331 Treble Cove Road
Building 300-2
North Billerica, MA 01862

Dear Ms. Lee:

Please refer to your supplemental new drug application (sNDA) dated May 18, 2020, received May 18, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DEFINITY®, Vial for (Perflutren Lipid Microsphere) Injectable Suspension.

This Prior Approval supplemental new drug application provides for adding the room temperature formulation to the current DEFINITY® NDA 021064 while maintaining the currently approved refrigerated storage DEFINITY® formulation.

## APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling text for the Prescribing Information, , with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## CARTON AND CONTAINER LABELING

We acknowledge your **November 17, 2020,** submission containing final printed carton and container labeling.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Because none of these criteria apply to your application, you are exempt from this requirement.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at 301-796-1348..

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.
Director
Division of Imaging and Radiation Medicine
Office of Specialty Medicine
Center for Drug Evaluation and Research

ENCLOSURES

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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11/17/2020 04:48:24 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 21-064/s024

# LABELING

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all of the information needed to use DEFINITY safely and effectively. See full prescribing information for DEFINITY.**

**DEFINITY RT** (Perflutren Lipid Microsphere) Injectable Suspension, for intravenous use

**Initial U.S. Approval: 2001**

## WARNING: SERIOUS CARDIOPULMONARY REACTIONS

***See full prescribing information for complete boxed warning***

**Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration (5.1). Most serious reactions occur within 30 minutes of administration.**

- **Assess all patients for the presence of any condition that precludes DEFINITY RT administration (4).**
- **Always have resuscitation equipment and trained personnel readily available.**

**----------INDICATIONS AND USAGE----------**
DEFINITY RT is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

**----------DOSAGE AND ADMINISTRATION----------**
DEFINITY RT may be injected by either an intravenous bolus or infusion. The maximum dose is either two bolus doses or one single intravenous infusion.

The recommended bolus dose for activated DEFINITY RT is 10 microliters (microL)/kg of the activated product by intravenous bolus injection within 30 to 60 seconds, followed by a 10 mL 0.9% Sodium Chloride Injection, USP flush. If necessary, a second 10 microliters (microL)/kg dose followed by a second 10 mL 0.9% Sodium Chloride Injection, USP flush may be administered 30 minutes after the first injection to prolong contrast enhancement.

The recommended infusion dose for activated DEFINITY RT is via an intravenous infusion of 1.3 mL added to 50 mL of preservative-free 0.9% Sodium Chloride Injection, USP. The rate of infusion should be initiated at 4 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

See Full Prescribing Information for instructions on preparation and administration.

**----------DOSAGE FORMS AND STRENGTHS----------**
DEFINITY RT is supplied as a single patient use 2 mL RFID-tagged clear glass vial containing colorless, uniformly clear to translucent (hazy) viscous solution in packages of sixteen (16) single patient use vials.

**----------CONTRAINDICATIONS----------**
Do not administer DEFINITY RT to patients with known or suspected: Hypersensitivity to perflutren lipid microsphere or its components.

**----------WARNINGS AND PRECAUTIONS----------**
Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration. (5.1)

Serious acute hypersensitivity reactions have occurred in patients with no prior exposure to perflutren-containing microsphere products, including patients with prior allergic reaction(s) to polyethylene glycol (5.2, 6).

Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY RT administration and monitor all patients for acute reactions (5 1, 5.2).

**----------ADVERSE REACTIONS----------**
The most common adverse reactions (≥0 5%) are headache, back/renal pain, flushing, nausea, chest pain, injection site reactions, and dizziness (6).

**To report SUSPECTED ADVERSE REACTIONS, contact Lantheus Medical Imaging, Inc. at 1-800-362-2668 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

**See 17 for Patient Counseling Information.**

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*



* Sections or subsections omitted from the full prescribing information are not listed

# FULL PRESCRIBING INFORMATION

## WARNING: SERIOUS CARDIOPULMONARY REACTIONS

**Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration *[see Warnings and Precautions (5.1)]*. Most serious reactions occur within 30 minutes of administration.**

- **Assess all patients for the presence of any condition that precludes DEFINITY RT administration *[see Contraindications (4)]*.**
- **Always have resuscitation equipment and trained personnel readily available.**

# 1 INDICATIONS AND USAGE

Activated DEFINITY RT (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.

# 2 DOSAGE AND ADMINISTRATION

## 2.1 Important Administration Instructions

- DEFINITY RT is intended for administration only after activation in the VIALMIX RFID apparatus. Before injection, this product must be activated, diluted, and prepared according to the instructions outlined below. The VIALMIX RFID apparatus should be ordered from Lantheus Medical Imaging, 331 Treble Cove Road, North Billerica, MA, 01862. For customer orders call 1-800-299-3431.
- 13mm ViaLok (packaged separately) must be used in the dilution process of Definity RT.
- DEFINITY RT may be injected by either an intravenous bolus or infusion. Do not administer DEFINITY RT by intra-arterial injection *[see Warnings and Precautions (5.3)]*.
- The maximum dose is either two bolus doses or one single intravenous infusion. The safety of bolus and infusion dosing in combination or in sequence, has not been studied.

## 2.2 Dosage

Bolus

The recommended bolus dose for activated DEFINITY RT is 10 microliters (microL)/kg of the activated product by intravenous bolus injection within 30 to 60 seconds, followed by a 10 mL 0.9% Sodium Chloride Injection, USP flush. If necessary, a second 10 microliters (microL)/kg dose followed by a second 10 mL 0.9% Sodium Chloride Injection, USP flush may be administered 30 minutes after the first injection to prolong contrast enhancement.

Infusion

The recommended infusion dose for activated DEFINITY RT is via an intravenous infusion of 1.3 mL added to 50 mL of preservative-free 0.9% Sodium Chloride Injection, USP. The rate of infusion should be initiated at 4 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

## 2.3 Imaging Guidelines

After baseline non-contrast echocardiography is completed, set the mechanical index for the ultrasound device at 0.8 or below *[see Warnings and Precautions (5.4)]*. Then inject activated DEFINITY RT (as described above) and begin ultrasound imaging immediately. Evaluate the activated DEFINITY RT echocardiogram images in combination with the non-contrast echocardiogram images.

In a crossover trial of 64 patients randomized to both bolus and infusion using DEFINITY, the duration of clinically useful contrast enhancement for fundamental imaging was approximately 3.4 minutes after a 10 microL/kg bolus and was approximately 7.1 minutes during the continuous infusion of 1.3 mL activated DEFINITY in 50 mL 0.9% Sodium Chloride Injection, USP at a rate of 4 mL/min.

## 2.4 DEFINITY RT Activation, Preparation and Handling Instructions

**There are two formulations of perflutren lipid microspheres that have differences concerning storage and preparation. Follow the preparation and storage procedures, as well as directions for activation of DEFINITY RT carefully and adhere to strict aseptic procedures during preparation.**

1. Activate DEFINITY RT by shaking the vial for 45 seconds using a VIALMIX RFID device.

   Note: illustrations of this procedure are contained in the VIALMIX RFID User's Guide.

   Do not use this drug unless it has completed a full 45 second activation cycle in the VIALMIX RFID. DEFINITY RT will not be properly activated unless the full 45 second activation cycle is completed. Error messages will display if the vial is not properly activated. Do not reactivate the vial if VIALMIX RFID did not properly activate the vial. Never reactivate a successfully activated DEFINITY RT vial (see step 2). A VIALMIX RFID that is not functioning properly must never be used. Only use a vial activated from a properly functioning VIALMIX RFID. Refer to the VIALMIX RFID User's Guide to ensure that a properly functioning VIALMIX RFID is used.

2. Immediately after VIALMIX RFID activation, but no more than 15 minutes, place the activated vial in the upright position and remove the flip top cap. Insert the 13mm ViaLok (Vented Vial Access Device) into the center of the rubber stopper and push down until properly engaged and locked onto the vial.

3. Obtain a syringe containing 1.4 mL preservative-free 0.9% Sodium Chloride Injection, USP.

4. Attach the syringe containing 1.4 mL preservative-free 0.9% Sodium Chloride Injection, USP to the 13mm ViaLok luer-lok hub. Add 1.4 mL of preservative-free 0.9% Sodium Chloride Injection, USP to the activated DEFINITY RT vial. Do not inject air into the DEFINITY RT vial.

5. With the 13mm ViaLok still inserted and syringe attached, rapidly swirl the upright vial for 10 seconds to mix the contents. Activated and diluted DEFINITY RT appears as a milky white homogenous suspension with a presence of foam/bubbles.

6. The product must be used within 5 minutes of dilution. If not used within 5 minutes the microspheres should be resuspended by rapidly swirling the upright vial for 10 seconds before the product is withdrawn in a syringe.

7. The activated DEFINITY RT may be used for up to 4 hours from the time of dilution, with the 13mm ViaLok still attached, but only after the microspheres are resuspended by rapidly swirling the upright vial for 10 seconds.

8. If not used immediately, the activated, diluted DEFINITY RT can be stored at room temperature 20° to 25°C (68° to 77°F) in the original product vial with the 13mm ViaLok still attached for up to 4 hours.

9. Invert the vial and withdraw the activated milky white suspension through the 13mm ViaLok into the syringe. Do not inject air into the DEFINITY RT vial.

10. Use the product immediately after its withdrawal from the vial; do not allow the product to stand in the syringe.

11. For bolus dosing, withdraw appropriate volume based on patient weight (kg) for administration. For infusion dosing, dilute 1.3 mL Definity RT in 50 mL of preservative-free 0.9% Sodium Chloride Injection, USP. *[see Dosage 2.2]*.

Special Instructions for the DEFINITY RT Radio Frequency Identification (RFID)-Tagged Vial

Full instructions for use of VIALMIX RFID are provided on the VIALMIX RFID screen and User's Guide.

- The RFID tag allows for the exchange of product information such as activation time and activation rate.

- VIALMIX RFID will only activate DEFINITY and DEFINITY RT RFID-tagged vials. Function of the RFID technology is not dependent on vial orientation as it is placed in the VIALMIX RFID. If the RFID tag is damaged or otherwise non-functional, the VIALMIX RFID will notify the user and the vial with the nonfunctional RFID tag cannot be used to activate DEFINITY RT with VIALMIX RFID. Discard the nonfunctional RFID-tagged DEFINITY RT vial.

- Follow all manufacturers' guidelines and do not operate any part of the VIALMIX RFID and DEFINITY RT RFID-tagged vials within 6 inches (15 cm) of a pacemaker and/or defibrillator.

# 3 DOSAGE FORMS AND STRENGTHS

DEFINITY RT is supplied as a single patient use 2 mL RFID-tagged clear glass vial containing a colorless, uniformly clear to translucent (hazy) viscous solution in packages of sixteen (16) single patient use vials.

Prior to activation, the headspace of each vial contains 6.52 mg/mL octafluoropropane and the viscous solution contains 3.75 mg/mL of a lipid blend. After activation and dilution with 0.9% Sodium Chloride Injection, USP, each vial contains a maximum of 1.2 X $10^{10}$ perflutren lipid microspheres, and about 80 microL/mL (0.65 mg/mL) octafluoropropane *[see Description (11)]*.

# 4 CONTRAINDICATIONS

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

- Hypersensitivity to perflutren lipid microsphere or its components [see *Warnings and Precautions* (*5*) *and Description (11)*].

# 5 WARNINGS AND PRECAUTIONS

## 5.1 Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions including fatalities have occurred uncommonly during or shortly following perflutren-containing microsphere administration, typically within 30 minutes of administration. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias). Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY RT administration and monitor all patients for acute reactions.

The reported reactions include: fatal cardiac or respiratory arrest, shock, syncope, symptomatic arrhythmias (atrial fibrillation, tachycardia, bradycardia, supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia), hypertension, hypotension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing, loss of consciousness, and convulsions *[see Adverse Reactions (6)]*.

## 5.2 Hypersensitivity Reactions

In postmarketing use, serious hypersensitivity reactions were observed during or shortly following perflutren-containing microsphere administration including:

Shock, bronchospasm, throat tightness, angioedema, edema (pharyngeal, palatal, mouth, peripheral, localized), swelling (face, eye, lip, tongue, upper airway), facial hypoesthesia, rash,

urticaria, pruritus, flushing, and erythema have occurred in patients with no prior exposure to perflutren-containing microsphere products, including patients with prior allergic reaction(s) to polyethylene glycol *[see Adverse Reactions (6) and Description (11)]*. Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY RT administration and monitor all patients for hypersensitivity reactions.

### 5.3 Systemic Embolization

When administering DEFINITY RT to patients with a cardiac shunt, the microspheres can bypass filtering by the lung and enter the arterial circulation. Assess patients with shunts for embolic phenomena following DEFINITY RT administration. DEFINITY RT is only for intravenous administration; do not administer DEFINITY RT by intra-arterial injection *[see Dosage and Administration (2.1)]*.

### 5.4 Ventricular Arrhythmia Related to High Mechanical Index

High ultrasound mechanical index values may cause microsphere cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias. DEFINITY RT is not recommended for use at mechanical indices greater than 0.8 *[see Dosage and Administration (2)]*.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Serious Cardiopulmonary Reactions [see *Warnings and Precautions* (*5.1*)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (*5.2*)]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1716 subjects were evaluated in pre-market clinical trials of activated DEFINITY. In this group, 1063 (61.9%) were male and 653 (38.1%) were female, 1328 (77.4%) were White, 258 (15.0%) were Black, 74 (4.3%) were Hispanic, and 56 (3.3%) were classified as other racial or ethnic groups. The mean age was 56.1 years (range 18 to 93). Of these, 144 (8.4%) had at least one adverse reaction (Table 1). There were 26 serious adverse events and 15 (0.9%) subjects discontinued because of an adverse event.

Serious Adverse Reactions

Among the 1716 study patients, 19 (1.1%) suffered serious cardiopulmonary adverse reactions.

For all adverse reactions, the overall incidence of adverse experiences was similar for the <65 year age group and the > 65 year age group, similar in males and in females, similar among

all racial or ethnic groups, and similar for bolus and infusion dosing. Table 1 summarizes the most common adverse reactions.

**Table 1 New-Onset Adverse Reactions Occurring in ≥0.5% of All DEFINITY-Treated Subjects**

| | | DEFINITY (N=1716) |
|---|---|---|
| Total Number of Adverse Reactions | 269 | |
| Total Number of Subjects with an Adverse Reaction | 144 | (8.4%) |
| Body system<br>Preferred term | n | (%) |
| Application Site Disorders | 11 | (0.6) |
| Injection Site Reactions | 11 | (0.6) |
| Body as a Whole | 41 | (2.4) |
| Back/renal pain | 20 | (1.2) |
| Chest pain | 13 | (0.8) |
| Central and peripheral nervous system disorder | 54 | (3.1) |
| Headache | 40 | (2.3) |
| Dizziness | 11 | (0.6) |
| Gastrointestinal system | 31 | (1.8) |
| Nausea | 17 | (1.0) |
| Vascular (extracardiac) disorders | 19 | (1.1) |
| Flushing | 19 | (1.1) |

N=Sample size 1716 subjects who received activated DEFINITY

n=Number of subjects reporting at least one Adverse Reaction

Other adverse reactions that occurred in ≤0.5% of the activated DEFINITY-dosed subjects were:

**Body as a Whole:** Fatigue, fever, hot flushes, pain, rigors, and syncope

**Cardiovascular:** Abnormal ECGs, bradycardia, tachycardia, palpitation, hypertension and hypotension

**Digestive:** Dyspepsia, dry mouth, tongue disorder, toothache, abdominal pain, diarrhea and vomiting

**Hematology:** Granulocytosis, leukocytosis, leukopenia, and eosinophilia

**Musculoskeletal:** Arthralgia

**Nervous System:** Leg cramps, hypertonia, vertigo and paresthesia

**Platelet, Bleeding, and Clotting:** Hematoma

**Respiratory:** Coughing, hypoxia, pharyngitis, rhinitis and dyspnea

**Special Senses:** Decreased hearing, conjunctivitis, abnormal vision and taste perversion

**Skin:** Pruritus, rash, erythematous rash, urticaria, increased sweating, and dry skin

**Urinary:** Albuminuria

## 6.2 Postmarketing Experience

In a prospective, multicenter, open-label registry of 1053 patients receiving DEFINITY in routine clinical practice, heart rate, respiratory rate, and pulse oximetry were monitored for 30 minutes after DEFINITY administration. No deaths or serious adverse reactions were reported, suggesting that these reactions are unlikely to occur at a rate of more than 0.3% when DEFINITY is used according to recommendations.

The following adverse reactions have been identified during the post-marketing use of perflutren-containing microsphere products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Fatal cardiopulmonary and hypersensitivity reactions and other serious but non-fatal adverse reactions were uncommonly reported. These reactions typically occurred within 30 minutes of DEFINITY administration. These serious reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias *[see Warnings and Precautions (5.1, 5.2)]*.

Reported reactions included:

Cardiopulmonary

Fatal cardiac or respiratory arrest, shock, syncope, symptomatic arrhythmias (atrial fibrillation, tachycardia, bradycardia, supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia), hypertension, hypotension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing.

Hypersensitivity

Anaphylactic reaction, anaphylactic shock, bronchospasm, throat tightness, angioedema, edema (pharyngeal, palatal, mouth, peripheral, localized), swelling (face, eye, lip, tongue, upper airway), facial hypoesthesia, rash, urticaria, pruritus, flushing, erythema.

Neurologic

Coma, loss of consciousness, convulsion, seizure, transient ischemic attack, agitation, tremor, vision blurred, dizziness, headache, fatigue.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

Risk Summary

Available data from case reports with DEFINITY use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. DEFINITY RT has a very short half-life; therefore, administration of DEFINITY RT to a pregnant woman is not expected to result in clinically relevant fetal exposure. No adverse developmental outcomes were observed in animal reproduction studies with administration of activated DEFINITY in pregnant rats and rabbits during organogenesis at doses up to 8 and 16 times, respectively, the maximum human dose based on body surface area *(see Data)*.

All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

*Data*

*Animal Data*

DEFINITY was administered intravenously to rats at doses of 0.1, 0.3, and 1.0 mL/kg (approximately 0.8, 2.4, and 8 times the recommended maximum human dose based on body surface area); DEFINITY doses were administered daily from day 6 to day 17 of gestation. DEFINITY was administered intravenously to rabbits at doses of 0.1, 0.3, and 1.0 mL/kg (approximately, 1.6, 4.8, and 16 times the recommended maximum human dose based on body surface area); DEFINITY doses were administered daily from day 7 to day 19 of gestation. No significant findings on the fetus were observed.

## 8.2 Lactation

Risk Summary

There are no data on the presence of DEFINITY in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DEFINITY RT and any potential adverse effects on the breastfed infant from DEFINITY RT or from the underlying maternal condition.

## 8.4 Pediatric Use

The safety and effectiveness of activated DEFINITY RT have not been established in the pediatric population.

The safety of injecting activated DEFINITY RT in neonates and infants with immature pulmonary vasculature has not been studied.

The pharmacokinetics of activated DEFINITY RT in pediatric subjects has not been studied.

### 8.5 Geriatric Use

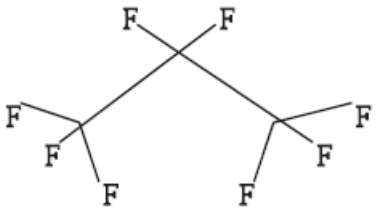
In clinical trials, the overall incidence of adverse reactions was similar for the <65 year age group and the ≥65 year age group. Of the total number of subjects in clinical trials of DEFINITY, 144 (33%) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects 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.

## 11 DESCRIPTION

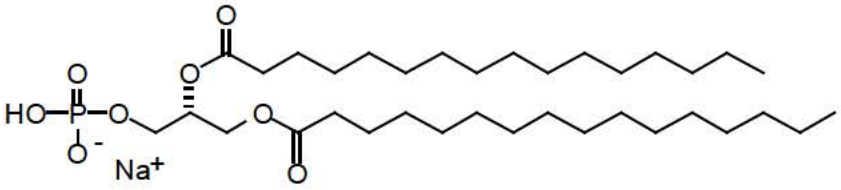
DEFINITY RT (Perflutren Lipid Microsphere) Injectable Suspension is an ultrasound contrast agent. The DEFINITY RT vial contains components that upon activation and dilution yield perflutren lipid microspheres. The unactivated vial contains a colorless, uniformly clear to translucent (hazy), viscous, sterile, non-pyrogenic solution, which upon activation with the aid of a VIALMIX RFID and dilution with 0.9% Sodium Chloride Injection, USP, provides a homogeneous, hypertonic, milky white injectable suspension of perflutren lipid microspheres. The suspension of activated DEFINITY RT is administered by intravenous injection.

The perflutren lipid microspheres are composed of octafluoropropane encapsulated in an outer lipid shell consisting of (R) – hexadecanoic acid, 1-[(phosphonoxy)methyl]-1,2-ethanediyl ester, monosodium salt (abbreviated DPPA); (R) - 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,4,9-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPC); and (R)-∝-[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]-5,7,11-trioxa-2-aza-6-phosphahexacos-1-yl]- ω-methoxypoly(ox-1,2-ethanediyl), monosodium salt; commonly called N-(**m**ethoxy**p**oly**e**thylene **g**lycol **5000** carbamoyl)-1,2-**di**-**p**almitoyl-sn-glycero-3-**p**hosphatidyl**e**thanolamine, monosodium salt (abbreviated MPEG5000 DPPE).

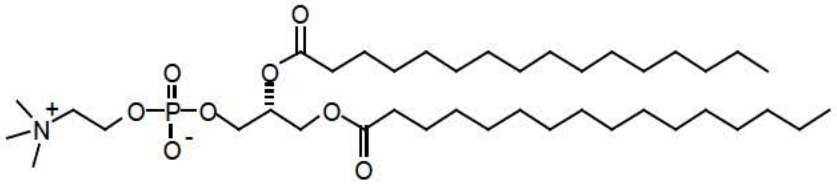
Octafluoropropane is chemically characterized as 1,1,1,2,2,3,3,3-octafluoropropane. It has a molecular weight of 188, empirical formula of $C_3F_8$ and has the following structural formula:



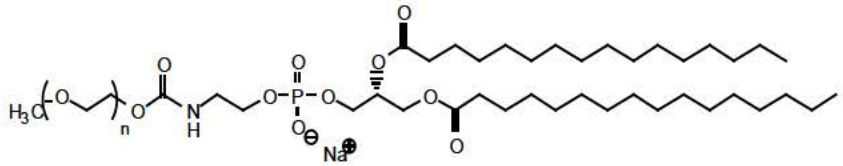
DPPA has a molecular weight of 670, empirical formula of $C_{35}H_{68}O_8PNa$, and following structural formula:



DPPC has a molecular weight of 734, empirical formula of $C_{40}H_{80}NO_8P$, and following structural formula:



MPEG5000 DPPE has an approximate molecular weight of 5750 represented by empirical formula $C_{265}H_{527}NO_{123}PNa$, contains <115ppm Ca2+ and the following structural formula:



Prior to activation, the DEFINITY RT vial contains 6.52 mg/mL octafluoropropane in the headspace which is confirmed by positive IR spectroscopic testing in every vial. Each mL of the viscous solution contains 3.75 mg lipid blend (consisting of 0.225 mg DPPA, 2.005 mg DPPC, and 1.520 mg MPEG5000 DPPE), 517.5 mg propylene glycol, 631 mg glycerin, 0.370 mg anhydrous sodium acetate, and 0.030 mg glacial acetic acid. The pH is 5.2 to 6.4. DEFINITY RT does not contain bacterial preservative.

After activating the contents of the vial in a VIALMIX RFID and diluting with 1.4 mL of preservative-free 0.9% Sodium Chloride, Injection, USP, each mL of the milky white suspension contains 0.045 mg DPPA, 0.401 mg DPPC, 0.304 mg MPEG5000 DPPE, 0.074 mg anhydrous sodium acetate, 0.006 mg glacial acetic acid, a maximum of $1.2 \times 10^{10}$ perflutren lipid microspheres, and about 80 microL/mL (0.65 mg/mL) octafluoropropane. The microsphere particle size parameters are listed in Table 2 below:

**Table 2 Microsphere Size Distribution**

| | Microsphere particle size parameters |
|---|---|
| Mean diameter range | 1.1 µm – 3.3 µm |
| Percent less than 10 µm | 98% |
| Maximum diameter | 20 µm |

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

Perflutren lipid microspheres exhibit lower acoustic impedance than blood and enhance the intrinsic backscatter of blood. These physical acoustic properties of activated DEFINITY RT provide contrast enhancement of the left ventricular chamber and aid delineation of the left ventricular endocardial border during echocardiography.

In animal models the acoustic properties of activated DEFINITY were established at or below a mechanical index of 0.7 (1.8 MHz frequency). In clinical trials, the majority of the patients were imaged at or below a mechanical index of 0.8.

## 12.3 Pharmacokinetics

Human pharmacokinetics information is not available for the intact or degassed lipid microspheres. The pharmacokinetics of octafluoropropane gas (OFP) was evaluated in healthy subjects (n=8) after the intravenous administration of activated DEFINITY at a 50 microL/kg dose.

### *Distribution*

OFP gas binding to plasma proteins or partitioning into blood cells has not been studied. However, OFP protein binding is expected to be minimal due to its low partition coefficient into whole blood.

### *Metabolism*

OFP is a stable gas that is not metabolized. The phospholipid components of the microspheres are thought to be metabolized to free fatty acids.

### *Elimination*

OFP was not detectable after 10 minutes in most subjects either in the blood or in expired air. OFP concentrations in blood were shown to decline in a mono-exponential fashion with a mean half-life of 1.3 minutes in healthy subjects.

*Special Populations*

The pharmacokinetics of octafluoropropane gas (OFP) was evaluated in subjects (n=11) with chronic obstructive pulmonary disease (COPD). The mean half-life of OFP in blood was 1.9 minutes. The total lung clearance of OFP was similar to that in healthy subjects.

The pharmacokinetics of activated DEFINITY RT has not been studied in subjects with hepatic diseases or congestive heart failure.

# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies with activated DEFINITY have not been performed to evaluate carcinogenic potential. Evidence of genotoxicity was not found in the following studies with activated DEFINITY: 1) bacterial mutagenesis assay (Ames assay), 2) *in vitro* mammalian mutagenesis assay, 3) *in vitro* human lymphocyte chromosome aberration assay, and 4) *in vivo* rat micronucleus assay.

Impairment of male or female fertility was not observed in rats and rabbits treated with activated DEFINITY at doses up to 24 and 15 times the human dose based on body surface area (in rats and rabbits respectively).

# 14 CLINICAL STUDIES

## 14.1 Echocardiography

A total of 249 subjects were evaluated in clinical trials (208 received activated DEFINITY and 41 placebo). In this group, 154 (61.8%) were male and 95 (38.2%) were female; 183 (73.5%) were White, 38 (15.3%) were Black, 21 (8.4%) were Hispanic, and 7 (2.8%) were classified as other racial or ethnic groups. The mean age was 53.9 years (range 18 to 87).

Activated DEFINITY was evaluated in four controlled clinical trials: Two open-label baseline controlled, unpaired blinded image evaluation studies and two identical placebo-controlled, unpaired blinded image evaluation studies. Subjects were eligible for these studies if they had two or more (of six) non-evaluable segments in either the apical 2- or 4-chamber view in non-contrast fundamental echocardiography.

In the baseline controlled studies, a total of 126 (67 in study A and 59 in study B) subjects received a bolus dose of 10 microL/kg activated DEFINITY. The outcome measures in these studies included the blinded assessment of ejection fraction (EF), endocardial border length (EBL) obtained by direct measurement, and qualitative assessment of wall motion.

In the two placebo-controlled studies a total of 123 subjects were randomized in 1:2 ratio to receive two intravenous bolus doses of either 0.9% Sodium Chloride Injection, USP (placebo) or activated DEFINITY 10 microL/kg (17 placebo vs. 33 activated DEFINITY patients and 24 placebo vs. 49 activated DEFINITY patients, respectively). The outcome measure for assessing the effectiveness of activated DEFINITY was the blinded assessment of improvement in

ventricular chamber enhancement (measured by videodensitometry at end-diastole and end-systole).

### *Endocardial Border Length*

As shown in Table 3, compared to baseline, a single bolus dose of 10 microL/kg of activated DEFINITY increased the length of endocardial border that could be measured at both end-systole and end-diastole. The mean change in border length from baseline at end-diastole was statistically significant for all readers in the apical 4-chamber view and for 3 out of 4 readers for the apical 2-chamber view. The mean change in border length from baseline at end-systole was statistically significant for 3 out of 4 readers for the apical 4-chamber view and for 2 out of 4 readers for the apical 2-chamber view.

### *Ventricular Chamber Enhancement*

Left ventricular chamber enhancement after an activated DEFINITY dose of 10 microL/kg was significantly increased from baseline compared to placebo in both views at the mid-ventricular and apical levels at end-diastole. Similar results were noted at end-systole, with the exception of the 4-chamber view.

### *Wall Motion*

In a retrospective analysis, in a subset of subjects (n=12 to 47, depending on reader) having at least 2 adjacent segments non-evaluable on non-contrast imaging, activated DEFINITY converted a baseline non-evaluable image to an evaluable image in 58 to 91% of the patients, depending on the reader. In the converted images, the accuracy of wall motion (i.e., normal versus abnormal) improved in 42 to 71% of the patients, depending on the reader, however, improvement in the specific diagnostic accuracy (e.g., hypokinetic, akinetic etc.) was not established. Also, in 13 to 37% of the patients, depending on the reader, activated DEFINITY was found to obscure the wall motion rendering the image non-evaluable.

### *Ejection Fraction*

In the 2 baseline controlled studies, ejection fraction results were evaluated in comparison to MRI. The results were evaluated by 3 blinded, independent radiologists. In these studies, although there was a statistically significant increase in ventricular chamber enhancement, activated DEFINITY did not significantly improve the assessment of ejection fraction compared to the baseline images.

**Table 3 MEAN (SD) ENDOCARDIAL BORDER LENGTH (CM) BY BOTH APICAL 2- AND 4-CHAMBER VIEWS AT END-SYSTOLE AND END-DIASTOLE BY STUDY, EVALUABLE SUBJECTS**

| Study/View | Endocardial Border Length – Blinded Read | | | |
|---|---|---|---|---|
| | Mean(SD) at End-Diastole | | Mean(SD) at End-Systole | |
| | Reader 1 | Reader 2 | Reader 1 | Reader 2 |
| **Study A: (N = 67)** | | | | |
| Apical 2-chamber | | | | |
| Baseline | 8.0(3.4) | 4.7(2.8) | 7.1(3.3) | 4.3(2.6) |

| | | | | |
|---|---|---|---|---|
| Post-DEFINITY | 12.8(5.2)* | 5.8(2.6)* | 10.6(5.0)* | 4.4(2.3) |
| Apical 4-chamber | | | | |
| Baseline | 8.1(3.3) | 4.5(2.6) | 7.6(3.2) | 4.5(2.7) |
| Post-DEFINITY | 13.5(5.2)* | 6.8(3.3)* | 11.5(4.4)* | 5.3(3.1) |
| **Study B: (N = 59)** | | | | |
| Apical 2-chamber | | | | |
| Baseline | 4.3(2.6) | 7.8(5.3) | 4.1(2.4) | 6.5(5.1) |
| Post-DEFINITY | 5.7(4.7)* | 8.2(6.5) | 5.5(4.4)* | 6.9(6.3) |
| Apical 4-chamber | | | | |
| Baseline | 4.0(2.7) | 9.2(5.9) | 3.8(2.6) | 7.3(5.6) |
| Post-DEFINITY | 7.1(5.5)* | 11.5(7.5)* | 5.9(5.3)* | 8.7(6.3)* |
| Activated DEFINITY Bolus Dose = 10 µL/kg<br>* Significant change from baseline (paired t-test, $p<0.05$) | | | | |

In an open administration, crossover trial, 64 patients were randomized to receive both bolus (10 microL/kg) and infusion (1.3 mL activated DEFINITY in 50 mL 0.9% Sodium Chloride Injection, USP at the rate of 4 mL/min) dosing of activated DEFINITY. Outcome measures for this study included clinically useful ventricular cavity enhancement and endocardial border length. Similar results were seen as described above.

Optimal activated DEFINITY doses and device settings for harmonic imaging have not been established.

### 14.2 Pulmonary Hemodynamic Effects

The impact of DEFINITY on pulmonary hemodynamics was explored in a prospective, open-label study of patients with normal (≤ 35 mmHg, 16 patients) and elevated (> 35 mmHg, ≤ 75 mmHg, 16 patients) pulmonary artery systolic pressure undergoing right heart catheterization. Patients with pulmonary artery systolic pressure greater than 75 mmHg were excluded from this study. Systemic hemodynamic parameters and ECGs were also evaluated. No clinically important pulmonary hemodynamic, systemic hemodynamic, or ECG changes were observed. This study did not assess the effect of DEFINITY on visualization of cardiac or pulmonary structures.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

DEFINITY RT is supplied as a single patient use 2 mL clear glass Radio Frequency Identification (RFID)-tagged vial containing a colorless, uniformly clear to translucent (hazy) viscous solution in packages of sixteen (16) single patient use vials.

- One (1) 2 mL RFID-tagged vial - NDC (11994-017-01)
- Sixteen (16) 2 mL RFID-tagged vials per kit - NDC (11994-017-16)

### 16.2 Storage and Handling

Store at Room Temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Regarding interference with medical devices, the RFID tag and VIALMIX RFID unit meets the IEC 60601-1-2 requirements for emission and immunity standards for medical devices.

## 17 PATIENT COUNSELING INFORMATION

Advise patients to inform their healthcare provider if they develop any symptoms of hypersensitivity after DEFINITY RT administration, including rash, wheezing, or shortness of breath.

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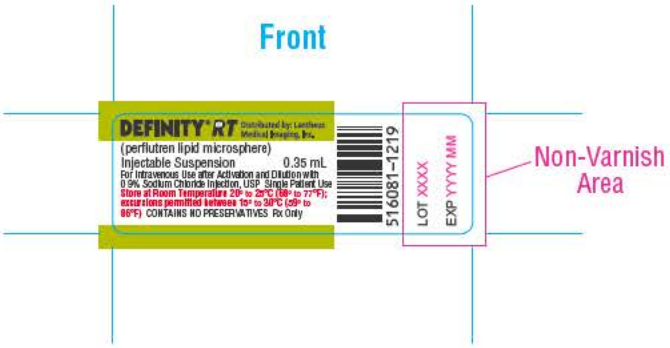
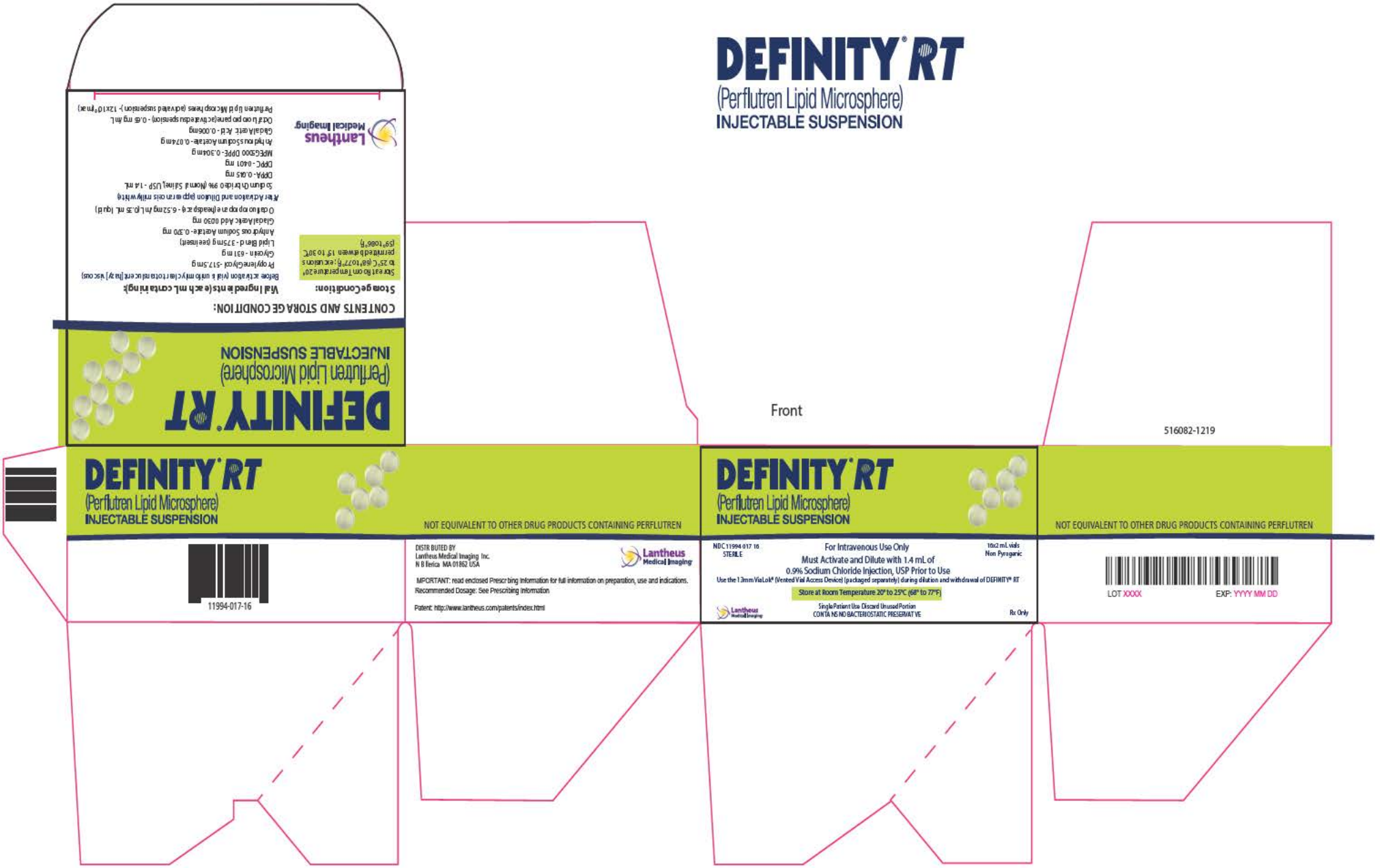
Lantheus Medical Imaging
331 Treble Cove Road
N. Billerica, Massachusetts 01862 USA
For ordering, tel. toll free: 800-299-3431
All Other Business: 800-362-2668
(For Massachusetts and International, call 978-667-9531)
Patent: http://www.lantheus.com/patents/index.html

516085-0120

**Note:** Keyline does not print.

TOP






13 mm ViaLok®
Vented Vial Access Device
For the dilution and withdrawal
of Activated DEFINITY® RT
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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-064/s024

# CLINICAL REVIEW

**PRIMARY CLINICAL/LABELING REVIEW**

| | |
|---|---|
| NDA | 021064 |
| Supplement Number | S-0024 |
| Sponsor | Lantheus Medical Imaging, Inc. |
| Product | Definity |
| Approved Indications | For use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. |
| Primary Reviewer | Stephanie Coquia |
| Team Leader | Alex Hofling |

**Review Team:**

CMC
Micro
OSE-DMEPA
CDRH
Pharm Tox
Clin Pharm

**PREVIOUS REGULATORY INTERACTIONS**

Meeting Package August 6, 2015
Meeting Package March 8, 2018
Type C Meeting April 25, 2018
Type C Meeting Package December 6, 2019

**DOCUMENTS REVIEWED**

Clinical review for Type C WRO Meeting January 2020
Type C WRO January 16, 2020
Definity RT draft PI, vial label, ViaLok label, and carton labels
(b)(4)
DMEPA Labeling Reviews
3.2.P.2.2 Drug Product

## BACKGROUND AND REGULATORY HISTORY

Lantheus Medical Imaging is proposing a formulation modification to DEFINITY® that supports room temperature storage, named DEFINITY RT®. The modification eliminates the [redacted] components of the current formulation ([redacted] and replaces the [redacted] with [redacted]. "[redacted] The proposed change reduces the liquid volume within the final drug product presentation [redacted] mL in the vial instead of [redacted] mL) and increases the liquid's viscosity. Activation of DEFINITY® requires use of the VIALMIX® device with a shaking speed of 4530 rpm for 45 seconds. As a result of the formulation change and increased viscosity, the shaking speed required for activation of DEFINITY RT® must increase to [redacted] rpm for 45 seconds. To accommodate these differences in shaking speed, Lantheus proposes the use of VIALMIX® RFID (S-0023) which will mix the vial of DEFINITY® or DEFINITY RT® according to the required speed. The device will recognize RFID tags on the vials of DEFINITY or DEFINITY RT®; the tags will have the required speed for that particular formulation encoded. As per S-0023, [redacted].

In addition, the activated microspheres need to be diluted with preservative-free saline prior to use. The Sponsor proposes [redacted]. The PAS includes a [redacted]. This device will be used to inject 1.4 mL saline into the activated vial.

The Sponsor plans to [redacted]

*Previous Regulatory Interactions on Room Temperature Formulation*

1. Type C Meeting to discuss this room temperature formulation and proposed commercialization program: scheduled for September 8, 2015 but cancelled following receipt of FDA's preliminary meeting comments
2. April 25, 2018 T-con regarding sterilization approach
3. WRO meeting comments January 16, 2020

The sponsor previously submitted a labeling supplement that included the VIALMIX® RFID device (Supplement S-0023), which received a complete response for device issues on September 5, 2019 and was resubmitted February 28, 2020. The S-0023 supplement was approved July 30, 2020.

## CLINICAL REVIEW

*In vivo performance of Definity RT*

No clinical data was submitted to support the formulation change. In the WRO, the following was communicated to the Sponsor: "You will need to provide adequate justification in support of your claim that the in vivo performance of the pre-and post-change drug product are similar, despite the formulation differences. You may include published literature references, available data, and other information to support your justification." This language was provided by Kimberly Raines of Biopharmaceutics Branch 3.

The equivalency evaluation was described in 3.2.P.2.2 Drug Product. Comparison of pre- vs. post-change formulations (DEFINITY and DEFINITY RT) included comparison of *in vitro* physicochemical data and *in vivo* studies in dogs.

The *in vitro* equivalency of DEFINITY RT to DEFINITY using three production lots of the post-change drug product and three commercial lots of the pre-change drug product was assessed by CMC and found acceptable, shown below. Table 2 (Microsphere Size Distribution) in the DEFINITY RT PI is identical to that in the DEFINITY PI.

**Table 3.2.P.2.2-25 Comparative Physicochemical Data for DEFINITY® and DEFINITY® RT: Final Vial Specifications**

| Attributes | Acceptance Criteria | JHS DEFINITY® Commercial Lots | | | SBL DEFINITY® RT Qualification Lots | | | |
|---|---|---|---|---|---|---|---|---|
| Final Vial Lot No. | | 6202B | 6203B | 6215 | 9104 | 9105 | 9106 | 9107 |
| Date of Manufacture | | 31 Jul 2017 | 29 Aug 2017 | 08 Jan 2018 | 07 Nov 2018 | 11 Nov 2018 | 15 Nov 2018 | 19 Nov 2018 |
| Batch Size (vials) | | (b)(4) | | | | | | |
| Size Distribution T=0 (Minimum-Maximum) | Mean microbubble diameter: 1.1 µm to 3.3 µm (b)(4) | (b)(4) | | | | | | |
| | | (b)(4) | | | | | | |

The *in vivo* studies in dogs included comparison of DEFINITY and DEFINITY RT:

- average mean left ventricle signal
- mean signal kinetics
- representative echocardiographic images

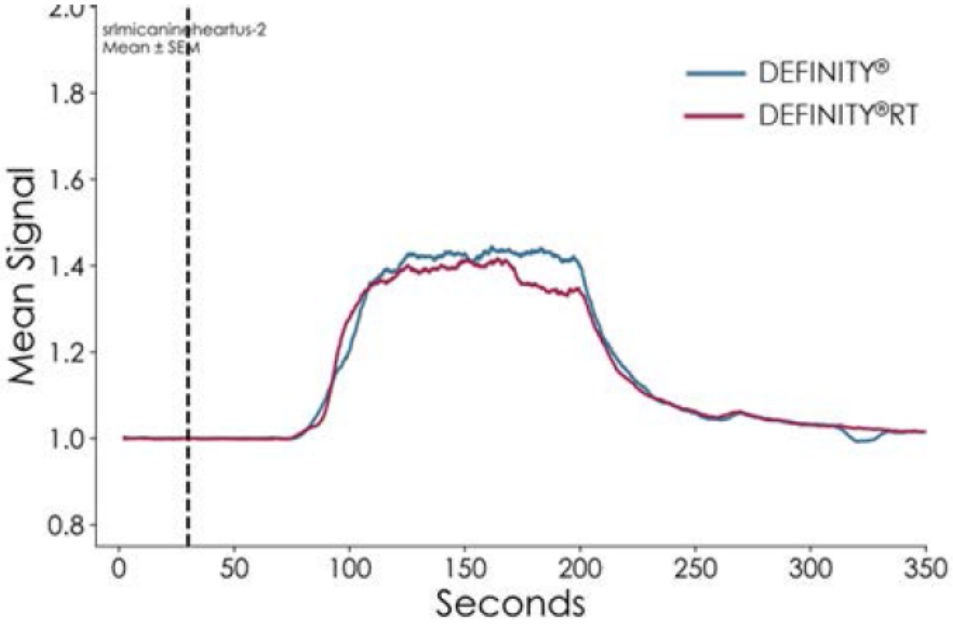
Representative results of demonstrating *in vivo* equivalency are shown below:

**Table 3.2.P.2.2-28 Average Mean Ventricle Signal for the Three (3) Lots of DEFINITY® and DEFINITY® RT[a]**

| Lot | DEFINITY® | Lot | DEFINITY® RT |
|---|---|---|---|
| 6204 | **79.9** ± 12.6 | 9105 | **82.2** ± 15.8 |
| 6211 | **80.9** ± 11.5 | 9106 | **81.2** ± 11.7 |
| 6212 | **79.6** ± 11.8 | 9107 | **77.8** ± 11.1 |

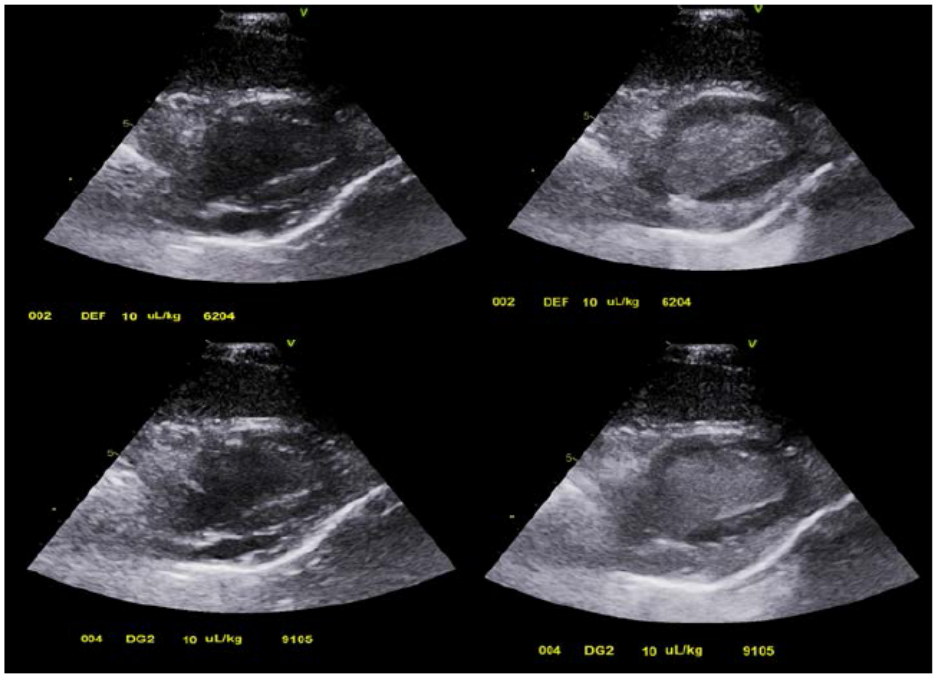
[a] Each value ± SD represents an average of n=3

**Figure 3.2.P.2.2-25 Plot of the Mean Values Derived from Ultrasound Imaging, Following Smoothing, for Infusions of DEFINITY® and DEFINITY® RT at Doses of 10 µL/kg**




Representative ultrasound images of DEFINITY® and DEFINITY® RT following a 10 µL/kg dose are shown in Figure 3.2.P.2.2-26 demonstrating similar contrast enhancement and endothelial border wall delineation.

**Figure 3.2.P.2.2-26 Representative Ultrasound Images of DEFINITY® (Top) and DEFINITY® RT (Bottom) Pre-dose (Left) and at Peak Contrast Enhancement During a 10 µL/kg Dose (Right)**




The equivalency evaluation was discussed with Clinical Pharmacology reviewer, Christy John. Based on the *in vivo* average mean ventricle signal results, mean signal kinetics, and representative echocardiographic images comparing Definity and Definity RT in dogs, Clinical Pharmacology has no concern that the *in vivo* imaging performance of Definity RT will be significantly different than that of Definity.

Based on the above *in vitro* and *in vivo* comparisons between DEFINITY and DEFINITY RT, the Clinical team also has no concerns about the imaging performance of DEFINITY RT as compared to DEFINITY.

Non-clinical also has no concern with the formulation change.

## LABELING REVIEW

*Potential for Medication and Storage Errors*

Potential medication and storage errors include:

- improper storage of DEFINITY RT or DEFINITY (i.e., refrigeration of DEFINITY RT or storage of DEFINITY at room temperature)

- wrong preparation errors (i.e., failure to dilute DEFINITY RT or dilution of DEFINITY).

Mitigation of the potential errors was achieved through labeling. See DMEPA review.

*Confirmation of the VIALMIX RFID functions*

VIALMIX RFID must be able to differentiate between DEFINITY RT and DEFINITY. It must also mix DEFINITY RT at the correct speed and alarm if the correct speed is not reached and/or maintained. These functions were reviewed by CDRH. CDRH also reviewed the PI and VIALMIX RFID documents and had no concerns.

*ViaLok Use*

DEFINITY RT must be diluted with 0.9% Sodium Chloride, USP, which is injected into the vial with ViaLok. CMC and PharmTox had no concerns with the extractables testing.

Following dilution, DEFINITY RT can be stored at room temperature for up to 4 hours with the ViaLok still attached prior to administration. Micro did not have any concerns with this change.

## LABELING NEGOTIATIONS

Recommended revisions for the PI, carton label, container label, and ViaLok label were sent to the Sponsor October 29, 2020, see Appendices 1 and 2. All changes were accepted by the Sponsor with one additional clarification regarding storage temperature conditions, which was found acceptable by CMC.

Additional revisions for the PI, carton label, and container label were requested on November 13, 2020, see Appendices 3 and 4. All changes were accepted by the Sponsor.

## APPENDICES

1. Tracked Changes PI – First Round
2. Labeling Revisions IR – First Round
3. Tracked Changes PI – Second Round
4. Labeling Revisions IR – Second Round
5. Clin Pharm comments regarding formulation change
6. Non-Clinical comments regarding formulation change
7. Micro comments on use of product 4 hours after dilution with ViaLok attached

APPENDIX 1

Seventeen (17) pages withheld as draft labeling (b)(4), immediately following this page.

APPENDIX 2

We reference S-024 for Definity RT. Please see attached PI with tracked changes and comments for recommended revisions. We also request confirmation on the volume of activated DEFINITY RT that must be diluted with 0.9% Sodium Chloride Injection, USP for infusion dosing.

In addition, we recommend the following be implemented prior to approval of this NDA SUPPLEMENT:

A. Vial Container Labels

1. We recommend revising the Definity RT product information in order to improve the readability of important information and removing the statement (b)(4) from the label. We recommend revising the label to read:

"Definity RT

(perflutren lipid microsphere)

Injectable suspension

For Intravenous Use after Activation and Dilution with 0.9% Sodium Chloride Injection, USP".

2. As currently presented, the storage requirement statement (b)(4) information on the label. In order to mitigate the risk of medication storage errors, we recommend increasing the prominence of the storage requirements statement through the use of bold font and red colored font. The revised storage requirement statement should read "**Store at Room Temperature at 25°C (77°F); excursions permitted between 15° and 30°C (59° to 86°F)**".

3. We recommend replacing the statement (b)(4) with "Single Patient Use".

4. We recommend removing the statement (b)(4) to increase readability of the rest of the information on the label.

5. The proposed vial container label does not contain a designated location for the lot number and expiration date. We recommend designating a location on the vial container label to provide this important information. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Definity RT Carton Labeling

1. As currently presented, the statement " (b)(4) is presented in front of the established name. We recommend removing this statement from the front of the established name.

2. The dosage form is presented under the established name in a small font size. We recommended increasing the size of the font for "Injectable Suspension" in order to increase its prominence.

3. We note that the statement [redacted] Rx Only" is prominently displayed on [redacted] We recommend removing the word [redacted] from this statement, decreasing the font size of "Rx Only" and moving the "Rx Only" statement to one of the bottom corners.

4. We note Definity RT requires activation and dilution prior to use. As currently presented, the front panel of the carton labeling contains the statement [redacted] In order to mitigate the risk of product confusion and preparation errors for Definity RT, we recommend increasing the prominence of this important information on the front panel. Additionally, we recommend revising the statement to read:

"For Intravenous Use Only

Must Activate and Dilute with 1.4 mL of 0.9% Sodium Chloride Injection, USP Prior to Use"

5. As currently presented, the [redacted] contains the statement [redacted] We recommend relocating this statement to the side panel of the labeling. Additionally, revise the statement [redacted] to read "Prescribing Information".

6. We recommend revising the statement [redacted] to read "Single Patient Use".

7. The [redacted] l of the proposed carton labeling display the storage conditions as [redacted] In order to avoid medication storage errors, we recommend making the storage requirements for Definity RT more prominent on the carton labeling. We recommend increasing the prominence of the storage information on the principal display panel. For example, a box may be utilized, font may be bolded, etc. to increase prominence. We also recommend the statement on the principal display panel to read "**Store at Room Temperature at 25°C (77°F)**". The other panel with the storage information should be revised to include temperature excursions. Revise to "**Store at Room Temperature at 25°C (77°F) excursions permitted between 15° and 30°C (59° to 86°F)**".

8. We note that the proposed carton labeling [redacted]. We recommend including a statement that states, "Use the ViaLok device (packaged separately) during dilution and withdrawal of Definity RT".

9. We note the proposed carton labeling does not contain a designated location for information on the lot number and expiration for Definity RT. Please indicate the intended location for the lot number and expiration date on the carton labeling. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are

used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

C. ViaLok Carton Labeling

1. As currently presented, the front panel of the proposed ViaLok carton labeling states that it is (b)(4) We note based on the prescribing information (PI) the ViaLok device is required for dilution and withdrawal. We recommend moving the statement to below the "Vented Vial Access Device" in similar font and revising this statement to read "for the dilution and withdrawal of Activated Definity RT".

Please respond by close of business November 5, 2020.

APPENDIX 3

Seventeen (17) pages withheld as draft labeling (b)(4), immediately following this page.

APPENDIX 4

We reference S-024 for Definity RT and your revisions sent November 5, 2020 for the PI and labeling. Please see attached PI with tracked changes for additional recommended revisions.

In addition, we recommend the following be implemented prior to approval of this NDA SUPPLEMENT:

A. General Comments for Vial Container Label and Carton Labeling

1. As currently presented the storage information is not consistent as the range is presented with a symbol (b)(4) as well as terms (b)(4) We recommend revising the storage temperature statement for consistency.
    a. Revise to "Store at Room Temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F)" on both the vial container label and the back panel of the carton labeling.
    b. Revise the principal display panel of the carton labeling to read "Store at Room Temperature 20° to 25°C (68° to 77°F)".

B. Definity RT Carton Labeling

1. We note the statement (b)(4) on the proposed principal display panel. We recommend revising this statement to read "16x2 mL vials" in order to align with the Definity RT Prescribing Information.
2. As currently displayed the carton contents state " (b)(4) We recommend removing this statement as this information is duplicative as the number of vials in the carton is presented on the principal display panel.
3. The usual dosage statement is missing from the carton labeling. We recommend adding "Recommended Dosage: See Prescribing Information".

Please respond by 9 AM EST November 16, 2020.

APPENDIX 5

| | |
|---|---|
| **From:** | John, Christy |
| **To:** | Coquia, Stephanie |
| **Cc:** | Hofling, August |
| **Subject:** | RE: NDA 021064 S-024 |
| **Date:** | Wednesday, November 04, 2020 4:35:26 PM |

As discussed, agree with you Stephanie.
Thanks for looping me in and taking my input and educating me in reading ultrasound ventricular border delineation.-

---

**From:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Sent:** Wednesday, November 04, 2020 3:38 PM
**To:** John, Christy <Christy.John@fda.hhs.gov>
**Cc:** Hofling, August <August.Hofling@fda.hhs.gov>
**Subject:** RE: NDA 021064 S-024

Hi Christy,

Thank you so much for talking with me today.

I intend to put this in my review, pending your concurrence. Alex – please also let me know if this language is sufficient.

> "The equivalency evaluation was discussed with Clinical Pharmacology reviewer, Christy John. Based on the *in vivo* average mean ventricle signal results, mean signal kinetics, and representative echocardiographic images comparing Definity and Definity RT in dogs, Clinical Pharmacology has no concern that the *in vivo* imaging performance of Definity RT will be significantly different than that of Definity."

Thank you,

Stephanie

---

**From:** John, Christy <Christy.John@fda.hhs.gov>
**Sent:** Wednesday, November 04, 2020 9:45 AM
**To:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Cc:** Hofling, August <August.Hofling@fda.hhs.gov>
**Subject:** RE: NDA 021064 S-024

Hi Stephanie,
I am not an expert in "bubble arena". I have gone briefly over the new formulation (b)(4) activation parameters, equivalence parameters, acoustic attenuation and zeta potential etc.
I will be happy to discuss this afternoon. However, I have a (b)(5)
I am open 1-2 PM, if that works for you.
Thanks
Christy

---

**From:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>

APPENDIX 6

**From:** Awe, Sunny
**To:** Coquia, Stephanie
**Cc:** Bhattacharyya, Sibaprasad
**Subject:** RE: Team/Start/Label Mtg./NDA 021064/S-024/ Definity/Lantheus/DMIP/Coquia/Fagbami -
**Date:** Thursday, October 01, 2020 9:31:57 AM

---

Hi Stephanie,

Thanks for your message on the Definity supplement.
Overall, there are no nonclinical concerns on either of the issues.

1. The compatibilty testing of Definity TR with ViaLok especially the extractable testing (section 3.2.P.2.6.6.5) suggests no potential safety risk based on the available data.
2. Nonclinical has no concern with the formulation change

Thank you

*Sunny*

---

**From:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Sent:** Wednesday, September 30, 2020 4:42 PM
**To:** Awe, Sunny <Sunny.Awe@fda.hhs.gov>
**Cc:** Bhattacharyya, Sibaprasad <Sibaprasad.Bhattacharyya@fda.hhs.gov>
**Subject:** RE: Team/Start/Label Mtg./NDA 021064/S-024/ Definity/Lantheus/DMIP/Coquia/Fagbami -

Hi Sunny,

I hope you are doing well.

I have two questions for you regarding this supplement, which is the supplement Lantheus submitted for a room temperature formulation of Definity. As an additional change, the Definity RT vial will be co-packaged with a transfer spike, called ViaLok (b)(4) (b)(4)

1. Included in this supplement is compatibility testing of Definity RT with the ViaLok, including extractables testing. Siba, our CMC reviewer, was wondering if you could review the results of the extractables testing for any non-clinical concerns. The pdf containing the extractables testing is attached (see page 52). Siba- feel free to respond to the email if you have anything more specific to add.

2. Any issues with the formulation change from a non-clinical perspective? I don't remember you bringing up anything at the team meeting start back in June. The Sponsor summarizes the formulation changes as follows, "(b)(4) Including this section of

the PAS which compares the differences in compositions of the formulations – see pages 4 and 5 of the second document. Siba – feel free to add any other information pertinent to the formulation change.

Thank you,

Stephanie

-----Original Appointment-----
**From:** Fagbami, Modupe <Modupe.Fagbami@fda.hhs.gov>
**Sent:** Friday, June 05, 2020 9:55 AM
**To:** Fagbami, Modupe; Marzella, Libero; Hofling, August; Coquia, Stephanie; Wang, Sue Jane; Zalkikar, Jyoti; Laniyonu, Adebayo A; Awe, Sunny; Bhattacharyya, Sibaprasad; Raghavachari, Ramesh; Marcsisin-Rogers, Renee; Kane, Devin; Mehta, Hina; Bui Nguyen, Tri; Neubauer, Marc; Patel, Sapana; Gorovets, Alex
**Cc:** Crich, Joyce
**Subject:** Team/Start/Label Mtg./NDA 021064/S-024/ Definity/Lantheus/DMIP/Coquia/Fagbami -
**When:** Monday, June 29, 2020 1:00 PM-2:00 PM (UTC-05:00) Eastern Time (US & Canada).
**Where:** Webex

# Team/Start Meeting
# NDA: 021064/S-024 Definity

**Meeting updated on 6/26/20 to add SharePoint link to Documents:** NDA 021064 S-024 Documents

**NDA**: NDA 021064/S-024
**Product:** DEFINITY®, Vial for (Perflutren Lipid Microsphere) Injectable Suspension.
**Sponsor:** Lantheus Medical Imaging, Inc.
**Indication:** Ultrasound Contrast Agent for Cardiology.
**Date of Submission**: 5/18/2020
**Date of Receipt**: 5/18/2020
**Filing Date:** 7/17/2020
**PDUFA due Date: Standard Review: 11/18/2020**

This supplemental application proposes the following changes:

- Adding the room temperature formulation to the current DEFINITY® NDA 021064 while maintaining the currently approved refrigerated storage DEFINITY® formulation .

APPENDIX 7

| | |
|---|---|
| **From:** | Marcsisin-Rogers, Renee |
| **To:** | Coquia, Stephanie |
| **Cc:** | Wells, Jesse |
| **Subject:** | FW: NDA-021064-SUPPL-24 Micro IR |
| **Date:** | Wednesday, October 28, 2020 2:02:09 PM |
| **Attachments:** | draft-labeling-text-tracked-changes.doc<br>image001.png |

Hi Stephanie,

I don't have any micro concerns that would affect the label.

Renee

---

**From:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Sent:** Wednesday, October 28, 2020 9:04 AM
**To:** Marcsisin-Rogers, Renee <Renee.Marcsisin-Rogers@fda.hhs.gov>
**Subject:** RE: NDA-021064-SUPPL-24 Micro IR

Hi Renee,

Sorry for the additional double-check – but do you have any micro concerns that would affect the label? I just assumed that the only micro issue from a labeling perspective would be the new reconstitution steps but just wanted to make sure. This is the latest version of the label. If you think of anything else, please let me know by the end of the day.

Thank you,

Stephanie

---

**From:** Marcsisin-Rogers, Renee <Renee.Marcsisin-Rogers@fda.hhs.gov>
**Sent:** Monday, October 26, 2020 3:34 PM
**To:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Cc:** Wells, Jesse <Jesse.Wells@fda.hhs.gov>
**Subject:** RE: NDA-021064-SUPPL-24 Micro IR

Hi Stephanie,

It doesn't change our response.

Thanks!

Renee

---

**From:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Sent:** Monday, October 26, 2020 2:47 PM
**To:** Marcsisin-Rogers, Renee <Renee.Marcsisin-Rogers@fda.hhs.gov>
**Cc:** Wells, Jesse <Jesse.Wells@fda.hhs.gov>
**Subject:** RE: NDA-021064-SUPPL-24 Micro IR

Hi Renee and Jesse,

Thank you so much!

I realized I forgot to add a few words in the version I sent previously, it should read:

1. The activated DEFINITY RT may be used for up to 4 hours from the time of dilution, with the 13mm ViaLok still attached, but only after the microspheres are resuspended by rapidly swirling the upright vial for 10 seconds.

2. If not used immediately, the activated, diluted DEFINITY RT can be stored at room temperature (25℃) in the original product vial with the 13mm ViaLok still attached.

I'm thinking that shouldn't change your response since you seemed okay with #1.

Thanks!

Stephanie

---

**From:** Marcsisin-Rogers, Renee <Renee.Marcsisin-Rogers@fda.hhs.gov>
**Sent:** Monday, October 26, 2020 2:35 PM
**To:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Cc:** Wells, Jesse <Jesse.Wells@fda.hhs.gov>
**Subject:** RE: NDA-021064-SUPPL-24 Micro IR

Hi Stephanie!

I spoke with my secondary Jesse, who is cc'd on the email, and we don't have any concerns with the language in the label.

Renee

---

**From:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Sent:** Thursday, October 22, 2020 3:54 PM
**To:** Marcsisin-Rogers, Renee <Renee.Marcsisin-Rogers@fda.hhs.gov>
**Subject:** RE: NDA-021064-SUPPL-24 Micro IR

Hello Renee!

Sorry to hear that. I am sure you are so relieved to have your computer.

Thanks for taking a look!

Stephanie

---

**From:** Marcsisin-Rogers, Renee <Renee.Marcsisin-Rogers@fda.hhs.gov>
**Sent:** Thursday, October 22, 2020 3:48 PM
**To:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Subject:** RE: NDA-021064-SUPPL-24 Micro IR

Hi Stephanie,

I spilt a smoothie on my computer last Wednesday, so I have been offline since then. I finally received a new

computer and got online this afternoon. I will look at their response and get back to you shortly.

Renee

---

**From:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Sent:** Wednesday, October 21, 2020 8:09 AM
**To:** Marcsisin-Rogers, Renee <Renee.Marcsisin-Rogers@fda.hhs.gov>
**Subject:** RE: NDA-021064-SUPPL-24 Micro IR

Hi Renee,

I am know you are still probably reviewing the Sponsor's responses to your latest IR, but any chance you have looked at their response to the sterile barrier question?

Just wanted to see if you had any concerns with this language in the label (i.e., that you were okay from a micro perspective that the Definity RT vial is sitting with the ViaLok attached for up to 4 hours prior to administration):

3. The activated DEFINITY RT may be used for up to 4 hours from the time of dilution, with the 13mm ViaLok still attached, but only after the microspheres are resuspended by rapidly swirling the upright vial for 10 seconds.

4. If not immediately (b)(4), diluted DEFINITY RT can be stored at room temperature (25℃) in the original product vial with the 13mm ViaLok still attached.

Thank you,

Stephanie

---

**From:** Marcsisin-Rogers, Renee <Renee.Marcsisin-Rogers@fda.hhs.gov>
**Sent:** Monday, September 21, 2020 11:42 AM
**To:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Subject:** FW: NDA-021064-SUPPL-24 Micro IR

Hi Stephanie,

The sponsor's responses to our IRs were not adequate. We are issuing more IRs (including the (b)(4) IR) with a 10 day response due date.

Renee

---

**From:** Coquia, Stephanie <Stephanie.Coquia@fda.hhs.gov>
**Sent:** Friday, September 11, 2020 1:58 PM
**To:** Marcsisin-Rogers, Renee <Renee.Marcsisin-Rogers@fda.hhs.gov>
**Subject:** RE: NDA-021064-SUPPL-24 Micro IR

You too!

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/s/

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STEPHANIE F COQUIA
11/16/2020 10:46:17 AM

AUGUST A HOFLING
11/16/2020 11:31:44 AM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-064/s024

# OTHER REVIEWS

# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | November 18, 2020 |
| Requesting Office or Division: | Division of Medical Imaging and Radiation Medicine (DMIRM) |
| Application Type and Number: | NDA 021064/S-024 |
| Product Name and Strength: | Definity RT (perflutren lipid microspheres) injectable suspension, 2 mL |
| Applicant/Sponsor Name: | Lantheus Medical Imaging (Lantheus) |
| OSE RCM #: | 2020-1056-2 |
| DMEPA Safety Evaluator: | Devin Kane, PharmD |
| DMEPA Team Leader: | Hina Mehta, PharmD |

## 1 PURPOSE OF MEMORANDUM

Lantheus Medical Imaging submitted revised vial container label and carton labeling on November 17, 2020 for Definity RT (perflutren lipid microspheres) injectable suspension NDA 021064/S-024. We reviewed the revised container label and carton labeling for Definity RT (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

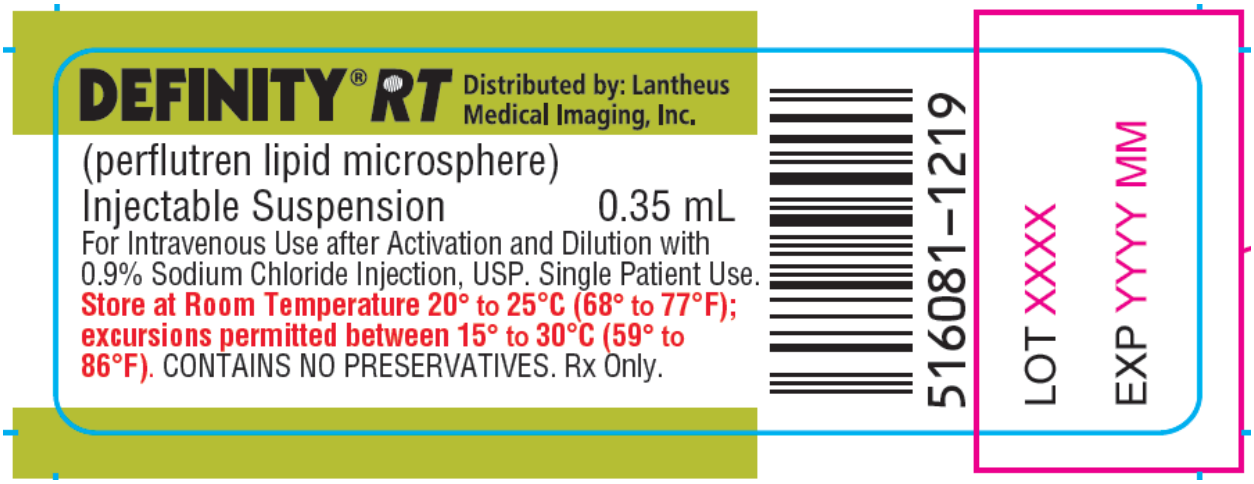
## 2 CONCLUSION

Lantheus Medical Imaging implemented all of our recommendations and we have no additional recommendations at this time.

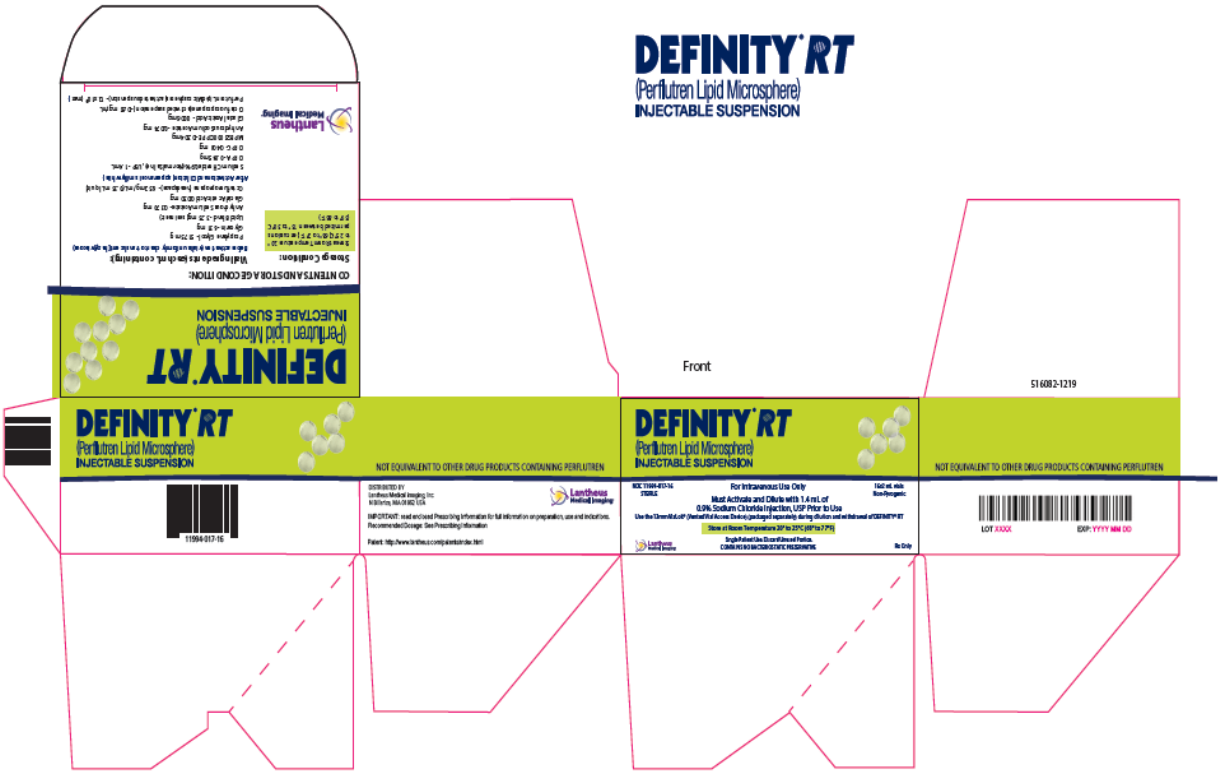
[a] Kane, D. Label and Labeling Review for Definity RT (NDA 021064/S-024). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 12. RCM No.: 2020-1056-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 17, 2020

- Vial Container Label




- Definity RT Carton labeling



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/s/

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DEVIN R KANE
11/18/2020 09:18:49 AM

HINA S MEHTA
11/18/2020 09:42:57 AM

# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | November 10, 2020 |
| Requesting Office or Division: | Division of Medical Imaging and Radiation Medicine (DMIRM) |
| Application Type and Number: | NDA 021064/S-024 |
| Product Name and Strength: | Definity RT (perflutren lipid microspheres) injectable suspension, 2 mL |
| Applicant/Sponsor Name: | Lantheus Medical Imaging (Lantheus) |
| OSE RCM #: | 2020-1056-1 |
| DMEPA Safety Evaluator: | Devin Kane, PharmD |
| DMEPA Team Leader: | Hina Mehta, PharmD |

## 1 PURPOSE OF MEMORANDUM

Lantheus Medical Imaging submitted revised the vial container label, carton labeling, and ViaLok carton labeling on November 5, 2020 for Definity RT (perflutren lipid microspheres) injectable suspension NDA 021064/S-024. We reviewed the revised vial container label, carton labeling, and ViaLok carton labeling for Definity RT (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 CONCLUSION

Lantheus implemented all of our recommendations for the proposed ViaLok carton labeling, and we have no additional recommendations at this time. The revised vial container label and carton labeling are unacceptable from a medication error perspective. We note there are inconsistences present on the proposed vial container label and carton labeling. Additionally, we note the carton labeling defines the package type as (b)(4)

[a] Kane D. Label and Labeling Review for Definity RT (NDA 021064/S-024). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 7. RCM No.: 2020-1056-1.

## 3 RECOMMENDATIONS FOR LANTHEUS MEDICAL IMAGING

We recommend the following be implemented prior to approval of this NDA SUPPLEMENT:

A. General Comments for Vial Container Label and Carton Labeling
   1. As currently presented the storage information is not consistent as the range is presented with a symbol (b)(4) as well as terms (b)(4) We recommend revising the storage temperature statement for consistency. Revise to "Store at Room Temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F)" on both the vial container label and the back panel of the carton labeling. Revise the principal display panel of the carton labeling to read "Store at Room Temperature 20° to 25°C (68° to 77°F)".

B. Definity RT Carton Labeling
   1. We note the statement (b)(4) on the proposed principle display panel. We recommend revising this statement to read "16x2 mL vials" in order to align with the Definity RT Prescribing Information.
   2. As currently displayed the carton contents state (b)(4) We recommend removing this statement as this information is duplicative as the number of vials in the carton is presented on the principal display panel.
   3. The usual dosage statement is missing from the carton labeling. We recommend adding "Recommended Dosage: See Prescribing Information".

Two (2) pages withheld as draft labeling (b)(4), immediately following this page.

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/s/

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DEVIN R KANE
11/12/2020 02:33:39 PM

HINA S MEHTA
11/12/2020 04:35:07 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 21-064/s024

# PROPRIETARY NAME REVIEW

**PROPRIETARY NAME REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

| | |
|---|---|
| **Date of This Review:** | August 24, 2020 |
| **Application Type and Number:** | NDA 021064/S-024 |
| **Product Name and Strength:** | Definity RT (Perflutren Lipid Microsphere) Injectable Suspension, 2 mL |
| **Product Type:** | Single Ingredient Product |
| **Rx or OTC:** | Prescription (Rx) |
| **Applicant/Sponsor Name:** | Lantheus Medical Imaging (Lantheus) |
| **Panorama #:** | 2020-40337949 |
| **DMEPA Safety Evaluator:** | Devin Kane, PharmD |
| **DMEPA Team Leader:** | Hina Mehta, PharmD |
| **DMEPA Associate Director of Nomenclature and Labeling:** | Chi-Ming (Alice) Tu, PharmD, BCPS |

Contents

# 1 INTRODUCTION

This review evaluates the proposed proprietary name, Definity RT, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A respectively. Lantheus did not submit an external name study for this proposed proprietary name.

## 1.1 REGULATORY HISTORY

Definity (perflutren lipid microspheres) injectable suspension was approved on July 31, 2001 under NDA 021064 for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. Definity is to be stored between 2°C and 8°C (36°F to 46°F) and must be activated prior to use via the VIALMIX device.

Lantheus submitted NDA 021064 Supplement-024 proposing a room temperature formulation under the proprietary name Definity RT. On June 2, 2020, Lantheus submitted the proposed proprietary name, Definity RT, for review.

## 1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on June 2, 2020.

| Product Characteristics | Definity | Definity RT |
|---|---|---|
| Intended Pronunciation | Def-in-ity | Def-in-ity R-T (the modifier is pronounced R-T) |
| Active Ingredient | Perflutren Lipid Microspheres | |
| Indication of Use | 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. | |
| Route of Administration | Administered as either an intravenous bolus injection or as an intravenous infusion. | |
| Strength | 2 mL<br>• Prior to activation the headspace of each vial contains 6.52 mg/mL octafluoropropane (b)(4) After activation, each vial contains a maximum of 1.2 X $10^{10}$ perflutren lipid microspheres, (b)(4) | |
| Dosage Form | Injectable Suspension | |
| Dose and Frequency | Bolus:<br>• The recommended bolus dose for activated Definity is 10 microL/kg of the activated product by intravenous bolus injection within 30 to 60 seconds, followed by a | |

| | | |
|---|---|---|
| | 10 mL saline flush. If necessary, a second 10 microL/kg dose followed by a second 10 mL saline flush may be administered 30 minutes after the first injection to prolong contrast enhancement.<br>Infusion:<br>• The recommended infusion dose for activated Definity is via an intravenous infusion of 1.3 mL added to 50 mL of preservative-free saline. The rate of infusion should be initiated at 4 mL/min, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/min. | |
| How Supplied | Definity is supplied as a single use 2 mL clear glass vial containing clear liquid in packages of four (4) and sixteen (16) single-use vials.<br>• One (1) 2 mL vial – NDC (11994-011-01)<br>• Four (4) 2 mL vials per kit – NDC (11994-011-04)<br>• Sixteen (16) 2 mL vials per kit – NDC (11994-011-16) | Definity RT is supplied as a single use 2 mL clear glass Radio Frequency Identification (RFiD) tagged vial containing a colorless, uniformly clear to translucent (hazy) viscous solution in packages of one (1) and sixteen (16) single use vials. |
| Storage | Store **at refrigerated temperatures** between 2°C to 8°C (36°F to 46°F). | (b)(4) |

## 2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Definity RT.

### 2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Definity RT would not misbrand the proposed product. However, OPDP noted in their evaluation that the proposed modifier, 'RT', could represent an abbreviation for other words in the medical lexicon such as radiation therapist, radiologic technologist, reaction time, etc. OPDP deferred to the Division of Medication Error Prevention and Analysis (DMEPA) to determine if there are any safety concerns with the proposed modifier, 'RT'. The Division of Medical Imaging and Radiation Medicine (DMIRM) concurred with the findings of OPDP's assessment for Definity RT, and requested DMEPA to evaluate the modifier 'RT' from a safety perspective.

### 2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Definity RT.

### *2.2.1 United States Adopted Names (USAN) Search*

The proposed proprietary name, Definity RT, contains the United States Adopted Name (USAN) stem ' -ef-' in the infix position used by the USAN Council to indicate Fc fusion protein products (e.g., pege*f*inodutide).[a] Proprietary names should usually not incorporate USAN stems in the position that USAN designates for the stem[b].The use of a USAN stem within proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs, which may compromise patient safety. To reduce the potential for confusion, USAN stems should usually not be incorporated into proprietary names.

However, we determined that the two-letter stem '*-ef-*' is often not distinct enough to be recognized as a USAN stem. Additionally, based on our post marketing experience, we do not have the same safety concerns with the two-letter stems, including '*-ef-*' , that we have identified with three or more letter USAN stems.[c,d] Furthermore, we are not aware of any name confusion associated with the two letter stem '*-ef-*' from our routine post marketing surveillance of Definity that's been marketed since 2001.

Therefore, we do not object to the inclusion of the two-letter USAN stem '*-ef*-', incorporated into the proposed proprietary name Definity RT.

### *2.2.2 Components of the Proposed Proprietary Name*

Lantheus indicated in their submission that the proposed proprietary name, Definity RT, is representative of the existing product, Definity. The modifier, 'RT', is being proposed to represent the modified room temperature stable formulation of the product. This proprietary name is comprised of a root name and a modifier that do not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

### *2.2.3 Comments from Other Review Disciplines at Initial Review*

In response to the OSE, June 10, 2020 e-mail, the Division of Medical Imaging and Radiation Medicine (DMIRM) noted "that RT meant to indicate room temperature storage could be

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[a] USAN stem search conducted on June 10, 2020.

[b] Guidance for industry: Best practices in developing proprietary names for drugs. Draft Guidance May 2014. http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM39899

[c] Institute for Safe Medication Practices. Safety briefs: Aripiprazole or rabeprazole? ISMP Med Saf Alert Acute Care. 2003;8(8):1-3.

[d] Institute for Safe Medication Practices. Safety Briefs. ISMP Med Saf Alert Acute Care. 2002;7(17):1-2.

interpreted as refrigerated temperature (especially for new users), which is how the current formulation should be stored". We assess the modifier in Section 2.2.26.

### *2.2.4 FDA Name Simulation Studies*

Eighty-seven (87) practitioners participated in DMEPA's prescription studies for Definity RT. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the prescription simulation studies.

### *2.2.5 Medication Error Data Selection of Cases*

On June 8, 2020, we searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving ***Definity*** that would be relevant for this review.

**Table 2. FAERS Search Strategy**

| FAERS Field | Search Terms |
|---|---|
| Initial FDA Receive Dates | 7/31/2001* to 06/01/2020 |
| Product Name | Definity |
| Verbatim Name(s) | --- |
| Product Active Ingredient | --- |
| Drug Role | Primary Suspect |
| Event | DMEPA Official PNR Name Confusion Search Terms |
| Country (derived) | USA |

*Definity Approval Date

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, 3 reports were not included in the final analysis for the following reasons:

*Confusion due to 'flu' in Established Name 'Perflutren' (n=1)*

1 case noted potential for confusion with flu vaccine because the name perfultren has "flu" in it. The case described other contributing factors such as changes in storage of flu vaccine.

*Wrong Technique (n=2)*

2 cases described wrong dose cases with possible wrong technique used. These medication errors were not caused by the proprietary name Definity.

Following exclusions, the search yielded no relevant cases.

### *2.2.6 Analysis of the Root Name and the Proposed Modifier 'RT'*

The proposed proprietary name is comprised of two words: the root name 'Definity' and the modifier 'RT'. The root name Definity is the approved proprietary name for the currently marketed version of the injectable suspension that must be stored refrigerated between 2°C and 8°C (36°F to 46°F).

Lantheus now proposes a formulation of perflutren lipid microsphere which is stored at room temperature (b)(4) The Applicant proposed to use the modifier "RT" to differentiate this formulation from the currently marketed formulation of Definity. See Table 1 under Section 1.2 of our review for a comparison of product characteristics between the proposed formulation and the currently marketed formulation.

Given Lantheus' proposal to use 'Definity' as the root name with the addition of a modifier, we considered the following: (1) use of the same root name, (2) the use of the modifier to differentiate the products, and (3) evaluation of the proposed modifier 'RT'.

1. **Evaluation of the use of the same root name 'Definity'**

   Definity has been marketed as the proprietary name for perflutren lipid microspheres since July 31, 2001. We note that the products share the same active ingredient and indication. We performed a FAERS search on June 8, 2020 to identify cases of name confusion with the root name Definity (See Section 2.2.5). Our search did not identify medication errors that could be attributed to name confusion involving Definity; thus, we do not object to the use of the same root name for this product.

2. **Evaluation of the use of a modifier to differentiate the products**

   Lantheus proposes to differentiate the proposed product from the currently marketed Definity by using the modifier 'RT' in the proprietary name nomenclature. It is not uncommon to use modifiers to denote a specific formulation or packaging configuration as part of a product line extension. The addition of a modifier to Definity may help to differentiate the proposed room temperature product from the currently marketed refrigerated product. However, we also note that omission and oversight of a modifier is cited in literature as a common cause of medication error.[e] Postmarketing experience shows that the introduction of product line extensions results in medication errors if the modifier is omitted and the product characteristics are similar or overlap.

   We considered the risk of name confusion if the modifier is dropped. We note that as part of this prior approval supplement, Lantheus also stated the proposed proprietary name "Definity RT" is only a part of a program being developed to minimize the risk of medication errors that may result from simultaneous availability of two branded products with different storage conditions. Lantheus's program also includes (b)(4)

[e] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. J Gen Intern Med. 2002; 17(8): 579-587.

[redacted] (b)(4)

Our evaluation finds the use of a modifier as a part of Lantheus's plan to distinguish the products reasonable and may further assist in differentiating the refrigerated and room temperature formulations.

3. **Evaluation of the proposed modifier 'RT'**

Lantheus indicated that the intended meaning of the modifier 'RT' is 'room temperature'. OPDP comments that 'RT' could represent an abbreviation for other words in the medical lexicon such as radiation therapist, radiologic technologist, reaction time, etc., and DMIRM commented that RT meant to indicate room temperature storage could be interpreted as refrigerated temperature (See Sections 2.1 and 2.2.3).

We searched our internal databases and did not identify any completed proprietary name reviews for names that contain this modifier. We note that the abbreviation 'RT' can be defined as "right", "route", "respiratory therapist", "respiratory therapy", "room temperature" or "round-trip".[f] The abbreviation 'RT' can also refer to many medical terms including but not limited to rectal temperature, room temperature, radiation therapy, Radiologic Technologist, etc.[g] We also searched the Institute of Safe Medication Practices' (ISMP) List of Products with Drug Name Suffixes[h] and found that the "RT" modifier already exists in drug nomenclature, such as Novoseven RT. We also note 'RT' is not on ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations.[i]

We acknowledge comments from OPDP and DMIRM and agree that the abbreviation 'RT' alone can represent many medical terms. However, our research found that when 'RT' is used as a modifier in drug nomenclature, its existing meaning is 'room temperature' and it is not an error-prone abbreviation when it comes to drug nomenclature.

Specifically, we note the modifier 'RT' in Novoseven RT is intended to mean "room temperature" and Novoseven RT can be stored at room temperature.[h] The proposed modifier 'RT' in Definity RT is also intended to mean "room temperature" and Definity RT can also be stored at room temperature. The use of this modifier in the proposed name is consistent with existing use. Thus, we find the modifier acceptable.

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[f] Merriam-Webster. "Rt". In Merriam-Webster.com medical dictionary. Retrieved 2020 AUG 14, available from https://www.merriam-webster.com/dictionary/rt#medicalDictionary

[g] Davis NM. Medical Abbreviations: 32,000 Conveniences at the Expense of Communication and Safety, 15th Edition, 2011.

[h] ISMP's List of Products with Drug Name Suffixes [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2010. Available from: https://www.ismp.org/sites/default/files/attachments/2018-04/drugnamesuffixes.pdf

[i] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2017. Available from: https://www.ismp.org/recommendations/error-prone-abbreviations-list

Based on the aforementioned reasons, DMEPA finds that the proprietary name 'Definity RT', although not free from the risk of error, is acceptable at this time. Furthermore, any residual risks of confusion between the formulations can be managed with labeling mitigation strategies that will be conveyed on our Label and Labeling review.

#### *2.2.7 Communication of DMEPA's Analysis at Midpoint of Review*

DMEPA communicated our findings to the Division of Medical Imaging and Radiation Medicine (DMIRM) via e-mail on August 20, 2020. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Medical Imaging and Radiation Medicine (DMIRM) on August 24, 2020, they stated no additional concerns with the proposed proprietary name, Definity RT.

## 3 CONCLUSION

The proposed proprietary name, Definity RT, is acceptable.

If you have any questions or need clarifications, please contact Tri Bui-Nguyen, OSE project manager, at (240)-402-3726.

### 3.1 COMMENTS TO LANTHEUS MEDICAL IMAGING

We have completed our review of the proposed proprietary name, Definity RT, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on June 2, 2020, are altered prior to approval of the marketing application, the name must be resubmitted for review.

## 4 REFERENCES


1. ***USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)***

   USAN Stems List contains all the recognized USAN stems.

## APPENDICES

### Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [j]

[j] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

| | Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance. |
|---|---|
| **Y/N** | **Is the proposed name obviously similar in spelling and pronunciation to other names?** |
| | Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products. |
| **Y/N** | **Are there inert or inactive ingredients referenced in the proprietary name?** |
| | Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)). |
| **Y/N** | **Does the proprietary name include combinations of active ingredients?** |
| | Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)). |
| **Y/N** | **Is there a United States Adopted Name (USAN) stem in the proprietary name?** |
| | Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem. |
| **Y/N** | **Is this proprietary name used for another product that does not share at least one common active ingredient?** |
| | Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name. |
| **Y/N** | **Is this a proprietary name of a discontinued product?** |
| | Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients. |

b. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the

proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

c. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

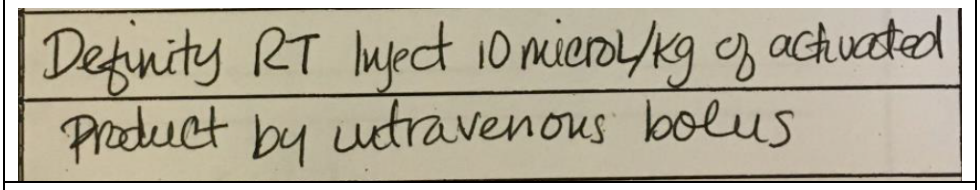
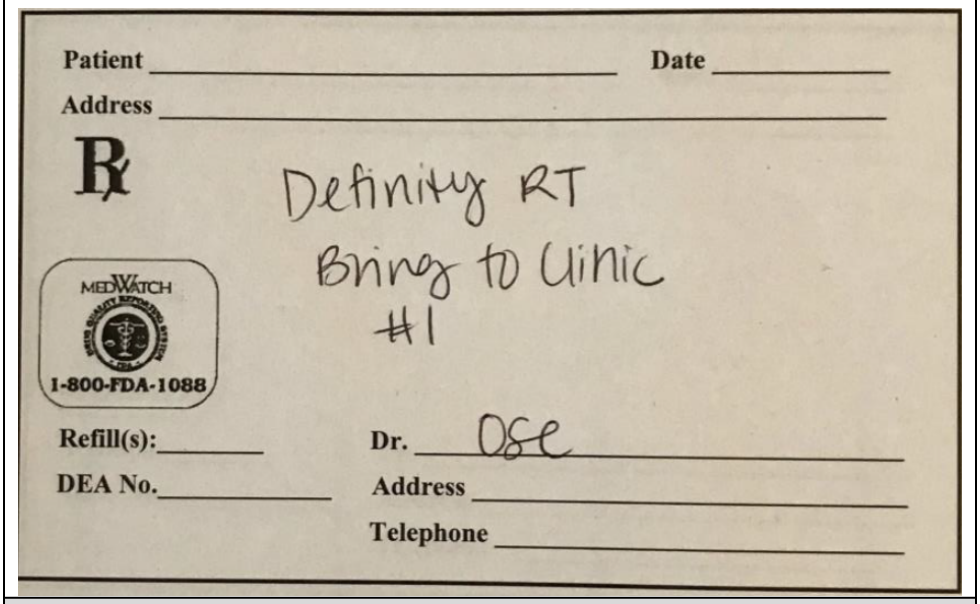
The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

## Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

**Appendix B: Prescription Simulation Samples and Results**

**Figure 1. Definity RT Study (Conducted on June 23, 2020)**

| Handwritten Medication Order/Prescription | Verbal Prescription |
|---|---|
| Medication Order:<br>  <br> | Definity RT<br>Bring to Clinic<br>#1 |
| Outpatient Prescription:<br>  <br> | |
| **CPOE Study Sample (displayed as sans-serif, 12-point, bold font)** | |
| Definity RT | |

**FDA Prescription Simulation Responses (Aggregate Report)**

207 People Received Study
87 People Responded

Study Name: Definity RT

| Total | 16 | 13 | 10 | 17 | |
|---|---|---|---|---|---|
| **INTERPRETATION** | **OUTPATIENT** | **CPOE** | **VOICE** | **INPATIENT** | **TOTAL** |
| DEFINITI RT | 0 | 0 | 1 | 0 | 1 |
| DEFINITY | 3 | 0 | 0 | 1 | 4 |
| DEFINITY RT | 28 | 15 | 6 | 24 | 73 |
| DEFINITYRT | 0 | 0 | 1 | 0 | 1 |
| DELFINITY RT | 1 | 0 | 0 | 0 | 1 |
| DESINITY | 0 | 0 | 1 | 0 | 1 |
| DIFFINITY RT | 0 | 0 | 3 | 0 | 3 |
| DIFINITY RT | 0 | 0 | 1 | 0 | 1 |
| DISFINITY RT | 0 | 0 | 1 | 0 | 1 |
| DYSFINITY RT | 0 | 0 | 1 | 0 | 1 |

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/s/

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