

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-064**

Administrative Documents

DEFINITY™
SECTION 13

**NEW DRUG APPLICATION NO. 21-064
PATENT INFORMATION ON ANY PATENT
WHICH CLAIMS THE DRUG**

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act [21 USC 355(b)(1)], the following patents include product claims for DEFINITY™, the drug that is subject of New Drug Application No. 21-064:

Patent Owner	U.S. Patent Number	Patent Title	Type of Patent	Expiration Date**
ImaRx Pharmaceutical Corporation	5,527,521	Low Density Microspheres and Suspensions and Their Use as Contrast Agents for Computed Tomography and In Other Applications	Compound and Method of Use	April 5, 2011
ImaRx Pharmaceutical Corporation	5,547,656	Low Density Microspheres and Their Use as Contrast Agents for Computed Tomography, and In Other Applications	Compound and Method of Use	April 5, 2011
DuPont Merck Pharmaceutical Company	5,769,080	Gas Filled Liposomes and Stabilized Gas Bubbles and Their Use As Ultrasonic Contrast Agents	Compound	July 20, 2010

** This date does not include any patent term extension under 35 U.S.C. 156.

**APPEARS THIS WAY
ON ORIGINAL**

**DEFINITY™
SECTION 14**

**NEW DRUG APPLICATION NO. 21-064
PATENT CERTIFICATION**

The undersigned declares that United States Patent Nos. 5,527,521, 5,547,656 and 5,769,080 cover the formulation, composition, and/or method of use of DEFINITY™. This product is the subject of this application for which approval is being sought.

DuPont Pharmaceuticals Company certifies that in its opinion and to the best of its knowledge, the patent information provided under 21 CFR 314.53 for United States Patent Nos.

5,527,521, 5,547,656 and 5,769,080 have not been submitted to the FDA.



Gerald J. Boudreaux, Ph.D., J.D.
Associate General Counsel

2 December 1998
Date

EXCLUSIVITY SUMMARY FOR NDA # 21-064 SUPPL # _____

Trade Name DEFINITY Generic Name Perflutren

Applicant Name DuPont HFD # 60

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?
YES / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

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

YES / / NO / /

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

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

d) Did the applicant request exclusivity?

YES / / NO / /

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

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

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES / / NO / /

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

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III ~~THREE-YEAR~~ EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for ~~three~~ years of exclusivity, an application or supplement must contain "reports of new clinical ~~investigations~~ (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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

YES / / NO / /

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

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

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

YES / / NO / /

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

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

YES / / NO / /

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

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /___/

If yes, explain: _____

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

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

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

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

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

Investigation #1 !

IND # ____ YES /___/ ! NO /___/ Explain: _____
! _____

Investigation #2 !

IND # ____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____
! _____
! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____
! _____
! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / /

If yes, explain: _____

MS
Signature

07/12/2001
Date

Title: _____

MS
Signature of Office/
Division Director

7/12/01
Date

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac



PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021064
Trade Name: DEFINITY (PERFLUTREN) 10UL/KG IV
Generic Name: PERFLUTREN
Supplement Number: 000 **Supplement Type:** N
Dosage Form:
Regulatory Action: AP **Action Date:** 7/31/01
COMIS Indication: TREATMENT OF CARDIOLOGY AND RADIOLOGY

Indication #1: For use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders

Label Adequacy: Other - see comments

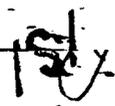
Formulation Needed: No new formulation is needed

Comments (if any) Pediatric language is added to the approvable letter so the sponsor can start to look into the pediatric issues

July 6, 2001: Sponsor has committed, April 4, 2001, to the post approval pediatric study schedule proposed in the January 22, 2001 letter from the Agency. Sponsor should submit a pediatric protocol within six months post approval.

Lower Range	Upper Range	Status	Date
4 kg	16 years	Deferred	1/31/02

This page was last edited on 7/6/01

Signature  H.D.
 Date 7/6/01



DuPont Pharmaceuticals Company

DEFINITY™

NEW DRUG APPLICATION NO. 21-064
AMENDMENT 6
DEBARMENT CERTIFICATION

In accordance with Section 306(k)(1) of the Food, Drug and Cosmetic Act (the Act), DuPont Pharmaceuticals Company hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Act in connection with this application.

Robert A. Morgan
Sr. Director, Regulatory Affairs

1/19/01

Date

000068

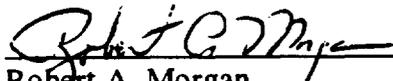


DuPont Pharmaceuticals Company

DEFINITY™

NEW DRUG APPLICATION NO. 21-064
DEBARMENT CERTIFICATION

In accordance with Section 306(k)(1) of the Food, Drug and Cosmetic Act (the Act), DuPont Pharmaceuticals Company hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Act in connection with this application.



Robert A. Morgan
Sr. Director, Regulatory Affairs

2/7/00
Date

APPENDIX

DEFINITY NDA 21-064
Clinical Team Leader Review

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NDA 21-064

Drug: Flufosphacele (USAN) lipid encapsulated perfluoropropane microbubble

Proposed Trade Name: Definity

Dosage Form: sterile non-pyrogenic liquid in a 2.0 mL glass vial

Proposed Dose: 10 µL/kg body weight

Route of Administration: intravenous

Method of Administration: bolus, slow over 30 to 60 sec. or infusion, 1.3 mL in 50 mL of preservative-free saline at a rate of 4 mL/min.

Strength: 6.0×10^7 to 1.2×10^{10} (1µm to 10µm)/mL

<u>Submission Type</u>	<u>Document Date</u>	<u>CDER Date</u>	<u>Assigned Date</u>
Original	08-Dec-99	10-Dec-99	10-Dec-99
Amendment (NC)	14-Apr-99	15-Apr-99	16-Apr-99
Amendment (BM)	13-May-99	14-May-99	17-May-99
Amendment (BM)	25-May-99	26-May-99	26-May-99
Amendment (BM)	23-Jun-99	24-Jun-99	29-Jun-99

Proposed Indication: (quoted)

Echocardiography

DEFINITY is indicated for contrast-enhanced ultrasound imaging of cardiac structures (ventricular chambers and endocardial borders).

Applicant: Du Pont Pharmaceuticals Company

Submitted: December 8, 1998

PDUFA Goal Date: September 24, 1999

due date

Review Team:

Chemistry – R. Kasliwal; Biopharmaceutics – D. Lee; Pharmacology/Toxicology – A. Laniyonu; Statistics – M. Sobhan; Clinical – J. Zolman; Project Manager – K. Cho.

Abstract:

This review provides a background of safety issues related to ultrasound contrast agents. It contains a review of safety submissions sent by the sponsor in answer to specific requests for electrocardiography (ECG) and for oxygen saturation data. Comment is provided on safety and efficacy. The sponsor chose magnetic resonance imaging (MRI) as the standard of truth for cardiac function.

Cardiac safety has not been adequately tested. ECG safety data, collected at baseline, during and immediately following dose administration, will allow an evaluation of cardiac safety.

The studies restricted enrollment of patients with serious COPD and/or CHF. These types of patients should be studied to evaluate the safety profile of DMP 115. The lack of oxygen saturation and ECG data is of concern in these patients. The minimal data for patients with COPD and CHF would need to be addressed in the labeling.

DMP 115 is approvable for ventricular cavity enhancement and endocardial border delineation/measurement.

Background:

Efficacy: - There are two intravenously administered ultrasound agents, Alunex and Optison manufactured by Molecular Biologics Inc. (MBI) that are approved for left ventricular (LV) opacification and endocardial border delineation (EBD). These agents are used off label to evaluate left ventricular function and regional wall motion. Both of these agents were originally submitted to the Center for Devices and Radiation Health (CDRH) following the completion of prospectively conducted clinical trials. After licensing approval of Alunex but before the NDA approval of Optison, these drugs were administratively transferred to the Center for Drug Evaluation and Research (CDER).

The sponsor of DEFINITY (DMP 115) seeks approval for the primary indications left ventricular cavity enhancement and endocardial border delineation.

Safety: - The contrast bubbles are microemboli with the primary impact organ being the microvasculature of the lung. The bubble (particle) size, concentration and total dose (initial and repeated doses in close time proximity) are crucial characteristics that will influence the safety profile.

The reviewer speculates that neonates and infants may be at risk since the pulmonary vasculature is not fully developed. Others at risk would be those patients with compromised pulmonary vasculature, e.g., those patients with pulmonary hypertension, such as COPD or CHF.

Pulse oximetry is a helpful method for monitoring pulmonary vascular drug effects particularly in those patients who have CHF and/or COPD. Emphasis has been placed on the collection of pre-dose pulse oximetry data, and monitoring for clinical signs such as dyspnea, during and at multiple times immediately post dose.

Comment: Chemistry data on DMP 115 'particle' size (bubbles) specifications are provided in Vol. 6, page 130, table 4.111. The size distribution following activation remains stable for 12 hours. Bubble size and concentrations are:

- 1 to <2 μ m: 5.0×10^7 to 1.0×10^{10} particles/mL*
- 2 to <6 μ m: 1.0×10^7 to 1.5×10^9 particles/mL*
- 6 to <10 μ m: $<5.0 \times 10^8$ particles/mL*
- >10 μ m: 5.0×10^7 particles/mL*

Particles >10µm may be embolic since they are larger than a red blood cell. The proportion of DMP 115 particles in size ranges larger than 10µm is not defined. The sponsor should further describe the size ranges and concentrations of particles.

The issue of pulmonary microembolism may extend to the myocardium and the central nervous system (CNS) if the particles pass through pulmonary filtering or bypass it in a right to left intracardiac shunt.

To better detect a drug effect on the myocardium, emphasis has been placed on the collection of electrocardiographic (ECG) data as close to the time of dosing as possible. An increase in the QTc interval of 30 to 60 msec was thought to be drug related while values above 60 msec raised concern about the potential for Torsades de Pointe (Committee For Proprietary Medicinal Products . Points To Consider: The Assessment of the Potential For QT Interval Prolongation By Non-Cardiovascular Medicinal Products, 17 December, 1997). It is now believed that any change in the QTc interval occurring after the intravenous administration of a drug is a warning of undesirable drug effect.

There is also concern about possible bioeffects induced by the mechanical force of the ultrasound on the microbubbles with the transfer of this energy to cells in contact with the microbubbles. This phenomenon is known as 'cavitation' and is related to the intensity and power derived from the ultrasound device. The sponsor has collected data related to the operative features of the devices used in the trials to support safety data in this NDA but has not analyzed this data for drug-device safety. No bioeffects were described with the devices that were used in the studies of DMP 115.

To further assess the embolic nature of these microbubbles emphasis has been placed on the product description data in the chemistry portion of the NDA submission. The characterization of the microbubble population with regard to size and the distribution of sizes, concentration, and fragility are vital points of information that influence safety. Products that require generation of microbubbles ('activation') immediately prior to use require evaluation of the method of activation and the resulting product.

Pulse oximetry data were obtained within minutes preceding and following the i.v. dose of DMP 115. The ECG data were collected one hour after the first dose and 30 minutes after the second dose in studies DMP 115-004 and DMP 115-005. These ECG time points are too delayed to detect early drug effects on the myocardium. Early events occurring in the myocardium are likely to be seen mainly in the population of patients who are the least clinically stable such as those with advanced COPD and/or CHF, i.e., those patients with pulmonary hypertension. The sponsor studied 12 COPD patients in a pharmacokinetic study (DMP 115-905) to be commented on later.

On April 2, 1999 the sponsor was asked for pulse oximetry data to include medical history and analysis of the ECG data (PR, QRS, and QTc parameters) to detect patients with drug related changes particularly increases of 30 milliseconds or more in the QTc interval. The sponsor provided this information for all pivotal studies on May 25, 1999.

Submission of April 14, 1999 was an example of data format sent in by the sponsor in preparation for the May 25, 1999 submission.

Sponsor's Submission Dated May 13, 1999.

Responding to Dr. Zolman's request of April 9, 1999, the sponsor provided tables of values for patients and normal subjects for all adverse drug effects (ADEs) and laboratory categories. The sponsor submitted: all ADEs for normal subjects and all patients including hematology, coagulation, and serum chemistry data. Also included were vital signs and ECG data. A total of 19 volumes were submitted.

Comment: Appendix A of this review a list is attached copied from this submission of patients who had a 30 msec increase in QTc interval for all the pivotal studies. The study number, site, patient number and the dose for studies 004 and 005 are listed.

In studies 004 and 005 where placebo or 5 or 10 μ L/kg doses were administered, a total of 68 patients had QTc values over 30 msecs. Of a total of 42 placebo patients in these two studies, 16 (38%) had abnormal QTc values while 167 patients who received DMP 115 there were 52 (31%) who experienced QTc abnormalities. This listing includes ECG values up to 72 hours. This is one more placebo patient and approximately 17 more DMP 115 patients than noted in the submission of May 25, 1999. Changes of less than 30 msec may possibly be related to a drug effect. A 30 msec level is an arbitrary choice to assess drug effect.

Many of the increased values occurred long after DMP 115 was administered. The sponsor may have missed DMP 115 induced QTc effects by not collecting ECG data immediately following administration of DMP 115

Review of Safety Data Submitted May 25, 1999:

The following sections (bolded and in quotations) are the sponsor's headings from the May 25, 1999 submission. Safety data are from pivotal Phase 3 studies DMP 115-004, 005, 006, 007, 009, 010, and 017. Phases 1 and 2 safety data (oxyhemoglobin and ECG) were requested and the sponsor submitted this selected safety data June 23, 1999.

“Summary By Site of 20% or Greater Changes in Vital Signs for all Pivotal Studies” page 000001.

The tables for each vital sign (pulse rate, systolic blood pressure, diastolic blood pressure) contain data related to dose, e.g., placebo, 5 μ L/kg, and 10 μ L/kg for studies DMP 115-004 and 005. The data is presented according to percentage change.

Comment: A 20% change is too large for either systolic or diastolic blood pressure to obtain sufficient sensitivity to change. These tables do not identify a class of patients that may be at cardio-pulmonary risk and do not indicate the presence of a safety problem.

“Summary by Site of 30 mSec or Greater Increases in QTc for all Pivotal Studies” page 000087.

Comment: The ECG data was collected 30 minutes after the last dose in the pivotal studies. This is too late to adequately detect an early cardiac drug effect. This data was reviewed to search for a delayed cardiac effect. Peak left ventricular contrast effect was noted to last about 120 seconds. The peak myocardial drug concentration probably occurs within the same time period.

This review searched for DMP 115 related QTc alterations at 30 minutes in studies DMP 115-004, 005, 006, and 007 where the drug doses of 5 and 10 μ L/kg were assessed. The

following table, prepared from the sponsor's data, summarizes the incidence of increases of 30 msec over baseline at 30 minutes post drug or placebo.

*** Table 1.**

QTc 30 msec Change Over Baseline 30 minutes post dose for Pivotal Studies

Study #	Placebo	DMP 115
DMP 115-004	2/18 (11%)	5/68 (7%)
-005	1/24 (4%)	10/99 (10%)
-006	no placebo (np)	11/67 (16%)
-007	np	4/59 (7%)
-009	np	4/104 (4%)
-010	np	8/95 (8%)
-017	np	dose 1: 8/64 (8%) dose 2: 6/63 (10%)

*From May 25, 1999 submission: summarized from values in Table 2.1 pages 000087 to 07.

It is noted that placebo related measurements had up to an 11% incidence of 30 msec increase in QTc interval measurements. It is uncertain whether the QTc increases after DMP 115 are drug related.

"O2 Saturation and Medical History Patient Listing" page 000098.

Pulse oximetry data for studies DMP 115-006, 007, 017, 902 were provided in tables for baseline, 3, 5, 10, 30, 60 (some studies included 15 and 45) minute intervals out to 24 hours. The table provides gender, age by increasing order, site, patient number, and history.

Comment: This data was requested to look for a DMP 115 effect on the pulmonary microvasculature that might result in a reduction of oxygen saturation due to an embolic effect interfering with pulmonary blood flow. This might be more pronounced for patients with pulmonary hypertension, CHF or COPD.

The following patients were identified as having a significant post-dose reduction in oxygen saturation within 3 minutes after DMP 115:

1. Study 006, site 1, patient #6, 61 year old woman had a baseline of 95% that fell to 90% at 3 minutes post 5µL/kg dose and fell further following the second 15µL/kg dose to as low as 87% remaining low for 60 minutes and returning to 94% by 24 hours. Hypertension, dilated cardiomyopathy, CHF, NYHA class 2.
2. Study 007, site 4, patient #6, 57 year old woman had a baseline of 98% fell to 92 at 3 minutes and to as low as 89% after the second dose recovering to 94 by 60 minutes after the second dose. COPD and hypertension.
3. Study 902, site C, patient #33, 36 year old man had a baseline of 95% fell to 91% at 3 minutes and recovered to 95% by 45 minutes post dose. No history of cardiac or pulmonary disease.
4. Study 902, site C, patient #36, 32 year old man with a baseline of 98% fell to 93 % and returned to 98% by 60 minutes. History of aortic stenosis with mild to moderate insufficiency.

Comment: These few cases are suggestive of an effect on pulmonary microvasculature. An inadequate number of patients with COPD and/or CHF were studied with DMP 115.

“Contingency Tables of QTc Vs O2 Saturation by: Any Timepoint, Any Timepoint by Gender, Corresponding Timepoints” page 000120.

The intent of this data listing was to attempt to identify any association of ECG abnormality with reduced oxygen saturation related to DMP 115. Two by two shift tables were requested to compare QTc (normal and abnormal) to O2 saturation (normal and abnormal). Tables were provided for studies DMP 115-006, 007, 017, 902 with data sorted by gender and at time pre- and post-dose.

Comment: This data was not of any help in identifying any trend related to QTc and O₂ saturation.

“Electrocardiogram Patient Listing and Dictionary” page 000162.

PR, QRS, and QTc are provided at baseline and at 30 minutes, 24, 48 and 72 hours. Study, age, gender, site, dose, ventilation rate, blood pressure and ECG findings are provided. The listing of “ventilation rate” values is incorrect and most likely represents “pulse rate” as the numbers range mostly from 60 to 90. The information provided did not include the clinical data to allow the reviewer to readily define the possible existence of a group of patients who might be at risk for ECG defined events following the administration of DMP 115 such as patients with CHF and/or COPD.

Comment. In Table 1 the number and percent of patients studied were noted. There are 15 fewer than in Table 2 since the latter does not include placebo patients with abnormal QTc values. Increases of 30 to 60 msec are thought to be drug related while values above 60msec are said to raise concerns about the potential for Torsades de Pointe (Committee For Proprietary Medicinal Products. Points to Consider: The Assessment of the Potential For QT Interval Prolongation By Non-Cardiovascular Medicinal Products, 17 December, 1997).

In the trials conducted by the sponsor there were no deaths or serious events that occurred in the proximity of the time of dosing with DMP 115. These QTc changes may have no clinical significance however further safety data is needed at intervals closer to the time following dose administration.

**APPEARS THIS WAY
ON ORIGINAL**

***Table 2.**

QTc Changes of 30msec+ Over Baseline Value At 30 minutes Post DMP 115

Age/Gender/Study	Site/Patient #	QTc: baseline/30 min	Change (msec)
F/59 004	9/6	365/400	35
F/87 004	6/5	392/430	38
M/58 004	1/9	397/434	37
M/75 004	2/1	432/466	134
F/31 005	4/22	432/479	47
M/41 005	3/17	448/490	42
M/46 005	1/3	401/433	32
M/52 005	4/17	388/431	43
M/69 005	3/2	410/501	91
M/69 005	3/7	412/445	33
M/72 005	3/6	408/443	35
M/75 005	5/12	388/436	48
F/29 006	3/5	270/425	155
F/37 006	2/8	433/486	53
M/31 006	2/1	380/433	53
M/66 006	2/15	400/441	41
M/75 006	1/26	367/406	39
M/26 007	4/18	420/455	35
M/56 007	3/2	376/415	39
M/65 007	1/6	409/459	50
F/70 009	1/207	388/426	38
M/45 009	8/204	367/399	32
M70 009	2/208	366/408	42
F/69 010	13/114	414/456	42
M/49 010	1/203	402/448	46
M/50 010	1/212	405/441	36
M/51 010	1/210	421/452	31
M/66 010	1/107	392/431	39
F/54 017	3/11	413/459	46
F/70 017	1/15	413/460	47
F/77 017	1/18	516/642	126
M/58 017	1/8	473/511	38
M/71 017	3/9	401/435	34
M/77 017	1/10	350/454	104
M/78 017	1/14	412/445	

*From Table 5.1, pages 000162 to 000259, May 25, 1999 submission.

Comment: Compared with Table 1, there are 15 fewer patients with QTc prolongation in Table 2. The difference is that Table 2. did not include the placebo dosed patients and in study 017, the 'dose 2' patients were not included because they were accounted for in the 'dose 1' count.

“ECG Shift Summary – PR, QRS, and QTc Intervals and QTc Interval by Gender”
page 000261.

Comment: This convenient presentation of data does not add to the present concern for attribution of the observed prolongation of QTc intervals found in patients studied in these trials.

“Summary of ECG Changes From Baseline” page 000306.

Comment: This data analysis is not helpful in distinguishing which patients had ECG changes and it will not be presented in this review.

“Summary of Drug Exposure and Number of ECGs Obtained” page 000313.

Comment: This listing provides information related to time periods in each study where ECGs were not collected as well as all that were completed for each study and the DMP 115 dose used in the study. This information does not contribute to this review. The concern is the timing of the collection of the ECG data.

Submission June 23, 1999: Requested safety data from Phases 1 and 2.

Data from the non-pivotal trials concerning oxyhemoglobin saturation and ECG abnormalities provided 12 cases where there was QTc prolongation within one hour after receiving DMP 115. Except for two patients, where a fall in oxygen saturation values are noted in Study 115-905 (described below), there are no new findings of oxygen saturation abnormality.

SAFETY (NDA data):

Pivotal trials vary as to use of placebo (placebo used in DMP 115-004, 005 and 902); varying doses (DMP 115-004, 005, 009, 010, 017); methods of dose (bolus undiluted, bolus diluted and infusion) as well as the timing of doses. The placebo was saline in studies 004 and 005 (Vol. 62, page 28) and in study 902 it was glycerol, propylene glycol and 0.9% saline (Vol. 109, page 24).

Other trials: Phase 1 studies DMP 115-900 and 901 are variable dose trials and 905 is a pharmacokinetic single dose trial. Phase 2 trials 001 and 903 are dose varying, repeat dose. Ongoing trials are:

Study 905 includes 12 normal subjects and 12 patients with COPD. The trial safety results Vol. 58, page 107, for “Individual Clinically Important Abnormalities” note that two COPD patients “experienced transient oxyhemoglobin desaturation” with values falling to SaO₂ of 88% at 5 minutes and 20 minutes after the DMP 115 dose for subjects #8 and #21 respectively. This was accompanied by dyspnea and tachycardia, in patient #8. Patient #21 was asymptomatic. Arterial oxyhemoglobin saturation tables are in Appendix D9 Vol. 201, pages 142 to 149.

Comment: Study 905 included 12 patients with COPD and suggests that two of the COPD patients were at risk for oxyhemoglobin desaturation. This finding is seen in one patient, in study DMP 115-007 patient #6 at study site 4, a 57 year old woman (mentioned above). The trials for DMP 115 have not included patients with a wide range of severity of cardio-pulmonary disease. The sponsor states “Patients with New York

Heart Association (NYHA) Class IV congestive heart failure (CHF) or severe chronic obstructive pulmonary disease (COPD) were not recruited. Exclusion of these patients was based on the protocol requirement of extended supine positioning necessary to complete all imaging sessions" Vol. 76, page 25. This is insufficient reason for excluding CHF/COPD patients from the Phase 3 trials. These CHF/COPD patients are the kind that will most likely have clinical need for ultrasound studies but there is not adequate data to support the safe use of DMP 115 in these severely ill patients. During a telephone conference on November 26, 1997, Dr. V. Raczowski, Deputy Director HFD-160, advised the sponsor that a "full range of disease is needed" (severity) in the patients studied.

Dosing and Safety:

Table 3. Dosing Used In Pivotal Trials (DMP 115-004, 005, 006, 007, 009, 010, 017)

Trial #	N	Placebo	Doses uL			Repeat	undil.	dil.	infuse
			5	10	other				
004	87	+	+	+	-	30+ min	+	-	-
005	124	+	+	+	-	30+ min	+	-	-
006	67	-	-	+	-	20 min	+	+/2mL	-
007	59	-	-	+	-	20 min	+	+/2mL	-
009	111	-	-	+	30	30-120 min	+	-	-
010	98	-	-	+	30	30-120 min	+	-	-
017	64	-	-	2x	1.3mL	24 hours	+	-	+50mL

Comment: The studies include repeat dosing which is important for labeling.

The design and variability in the dose, administration, timing and dilution of DMP 115 resulted in a range of safety data that supports the sponsor's recommended dose of 10 µL by slow bolus. The infusion dose of 1.3mL added to 50 mL of preservative-free saline for infusion was studied (DMP 115-017) in 64 enrolled (63 completed) patients. The infusion was given over a mean time of 7.5 minutes and the mean dose was 12.8µL/kg (range: 5.5 to 20.9µL/kg). There were 18 instances of QTc prolongation (more than 30msecs) that occurred in 15 patients but the relationship to the timing of dosing was not explained. The same patients also received two 10µL/kg doses on a separate day.

Comment: It is unclear whether or not the ECG abnormalities are related to the infusion. ~~The safety data does not support the method of infusion. The data does support the 10µL dose noted in the proposed package insert. There is evidence to support repeat doses but how many and how often is not stated by the sponsor. The ECG safety data suggests a DMP 115 cardiac effect and it is unknown whether this effect is prevalent during and/or shortly after dosing. The trials did not include seriously ill patients with COPD and/or CHF.~~

Narrative Summaries For: (Integrated Summary of Safety, Vol. 50, pages 161 to 176)

Deaths: Five deaths are reported all occurring remote to the time of drug administration and according to the sponsor, not precipitated by DMP 115.

Comment: I agree with the sponsor's conclusion.

Serious Adverse Experiences: Events occurred in 11 patients at a prolonged time following the dose and were related to disease rather than to DMP 115. With the exception of a case of fever occurring 24 hours after receiving DMP 115, The other cases occurred days to weeks after dosing.

Comment: These reports are not suspicious of drug related events.

Safety-Related Discontinuations: There were 10 discontinuations.

Comment: The events, suggesting CNS, cardiac or pulmonary involvement occurring shortly following the administration of DMP 115, are considered to be most important. The following patient, 9/203, study DMP 115-009, Vol. 92, page 154, is considered by this reviewer to be important because of the occurrence of dyspnea and chest pain.

A 29 year-old woman received a bolus of 10 μ L/kg i.v. of DMP 115 and 3 minutes later experienced moderate dyspnea and severe chest pressure. The dyspnea and chest pressure resolved within 3 minutes without treatment. The investigator attributed this event to DMP 115. There was no change in the ECG 24 hours post DMP 115.

Back pain, chest pain, headache and dizziness were signs of distress that prevailed in discontinued patients.

Comment: It is unknown whether or not these patients have sub-clinical signs and symptoms related to embolic events in the CNS, myocardium and/or lungs.

Clinical Laboratory Tests:

Clinical chemistries were evaluated at baseline and at 24 hours in all pivotal trials except for studies 004 and 005 where they were evaluated at 30 minutes post dose. Shift tables were examined (Vol. 50, Table 5, page 226 [max. post admin. values] for normal volunteers and for patients, page 307 [normal to high]). Several patients showed a glucose increase and others a minimal bilirubin increase. These changes are unlikely to be due to DMP 115 as they were not observed in more closely monitored Phase 1 studies. The change in glucose levels may be attributed to dietary effects in the 24 hours following the dose of DMP 115. The hematology and coagulation studies were not suggestive of any abnormality induced by DMP 115.

Comment: While this reviewer believes that only a minimal effect on laboratory results is attributable to DMP 115, Dr. Zolman believes that there is evidence, present in the line listings of the serum chemistries, of increases in values from the normal into the high range. I do not see a consistent effect that may be attributed to DMP 115. In study 900 Dr. Zolman notes rises in IgG in subjects. He discusses these issues in his clinical review. I do not know if these changes are due to DMP 115.

EFFICACY

Studies DMP 004 and 005 had two primary objectives: To demonstrate left ventricular cavity enhancement and to determine the safety of two i.v. doses of DMP 115.

The secondary objectives were to evaluate DMP 115 for: 1. Improvement of endocardial border delineation (EBD) in apical two and four chamber views. 2. Duration of ventricular cavity enhancement. quality of wall motion detection

Comment: These trials provide mainly testimonial evidence to support the objectives.

Duration of ventricular cavity enhancement consists of a record of time that enhancement was present. There is no common definition amongst the investigators in the trial as to what exact features were used to denote when enhancement began or stopped. Nevertheless the times are reported under two categories: "contrast observed (sec)" and "Clinically Useful Cavity Enhancement (sec)" see Vol. 42, page 197, Table 7. What "clinically useful" means is not defined in the study protocols so it is uncertain what the investigators were actually recording.

A significant difference was found between the 5 and 10 $\mu\text{L}/\text{kg}$ doses. The mean duration of enhancement for 10 $\mu\text{L}/\text{kg}$ was 98.7sec with a SD of 59.6sec.

Comment: The sponsor has provided data suggesting the duration of contrast in the left ventricle, using the 10 $\mu\text{L}/\text{kg}$ dose, will last from 60 to 120 seconds.

Ventricular cavity enhancement was assessed by blinded, independent readers using apical two and four chamber views. Saline placebo doses were also used but saline has a different appearance than activated DMP 115 so the blinding of the placebo doses is questioned. There is also videodensitometry data that is very convincing and is presented by M. Sobhan Ph.D., in the statistical review page 8, Table 2.1.B.4.

Comment: The blinded reads are supported by the objective videodensitometry readings that demonstrate a consistent change from baseline following DMP 115. The sponsor has supported the claim for left ventricular cavity enhancement.

Endocardial border delineation was demonstrated in study DMP 115-004 but not study 005. The statistical review, Table 2.1.B.3, compares the statistical validity of the two studies. Endocardial border **length** was supported by studies DMP 115-006 and 007. which ties in with the claim for endocardial border delineation.

Comment: The sponsor has demonstrated that DMP 115 can assist in endocardial border delineation and length.

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commercial

information

Endocardial border length (EBL) was found to be statistically supported in studies 006 and 007 (Table 2.2.B.3, page 14 statistics review) by the two trained readers but not by the reader without training. Endocardial border delineation improved in at least one segment in study 004 but not in study 005 (Table 2.1.B.3, page 7).

Comment: This evaluation (in studies 006 and 007) is based on objective measurement of improvement in defining the endocardial border (increase in centimeters) and reflects how important the method of measurement (reader training) is to this efficacy parameter. These three studies (out of four) support a claim for endocardial border delineation.

Wall motion (normal or hyperkinetic; hypokinetic; akinetic; dyskinetic) was graded by the readers, comparing baseline with post-dose images, and the results were compared with the MRI readings. The statistical review of this claim could not eliminate bias.

Comment: Whether images were read paired or unpaired there was little difference. DMP 115 showed a statistically supported improvement, for fundamental echocardiography, in the assessment of wall motion compared with MRI. This is a

qualitative evaluation that supports this claim of wall motion evaluation. Since MRI is not a proven standard for this claim, the claim cannot be verified.

Safety Conclusions:

Bubble Size:

The proportion of particles that are in size ranges larger than 10 μ m is not defined. The sponsor should further describe the size ranges and concentrations of particles above 10 μ m.

Placebo:

Both saline and drug 'vehicle' were used as placebo. The sponsor did not evaluate the data to determine if there was any difference in the safety data (AE reports, etc.) between the two.

Study Population:

The studies did not include patients with a wide severity range of cardio-pulmonary disease. The information provided did not include the clinical data to allow the reviewer to readily define the possible existence of a group of patients who might be at risk for ECG defined events following the administration of DMP 115 such as patients with pulmonary hypertension. These patients might be sensitive to blockage of the pulmonary microvasculature by a product that is even transiently in particle form. This has been found with technetium Tc-99m macroalbumin (used for lung perfusion scanning) and is noted in that product's package insert

ECG Abnormalities:

The ECG data was collected one hour after the first dose and 30 minutes after the second dose in studies DMP 115-004 and DMP 115-005. This is too delayed to detect possible early drug effects on the myocardium and its conduction system.

In studies 004 and 005 where placebo, 5 or 10 μ L/kg doses were administered, a total of 68 patients had QTc values over 30msec. Of a total of 42 placebo patients in these two studies, 16 (38%) had abnormal QTc values while 167 patients who received DMP 115 experienced 52 (31%) QTc abnormalities. This listing includes ECG values up to 72 hours. Many of the increased values are not an immediate effect however, the sponsor may have missed DMP 115 induced QTc effects by not collecting ECG data immediately following administration of DMP 115.

Adverse Events:

In the trials conducted by the sponsor there were no cardiac deaths or serious cardiac events that occurred in the proximity of the time of dosing with DMP 115.

Back pain, chest pain, headache and dizziness were signs of distress that prevailed in the discontinued patients. It is unknown whether or not these signs and symptoms are related to embolic events in the CNS, myocardium and/or lungs.

Two of 12 COPD patients in study DMP 115-905 experienced pulmonary symptoms with one having a transient fall in oxygen saturation. A study of patients with moderate to severe pulmonary hypertension is recommended.

Efficacy Conclusions:

Dose:

The design and variability in the dose, administration, timing and dilution of DMP 115 provides a range of safety data that supports the recommended dose of 10 μ L/kg by slow i.v. bolus. There is evidence to support the safety of repeat doses but how many and how often is not stated.

Duration of left ventricular contrast was greater with the 10 μ L/kg than the 5 μ L/kg dose. The mean duration of enhancement for 10 μ L/kg was 98.7sec with a SD of 59.6sec. The sponsor provided data to support the duration of contrast in the left ventricle to last from 60 to 120 seconds.

Cardiac Claims:

For studies DMP 115-004 and 005:

The blinded reads are subjective however, the readings are supported by the objective videodensitometry data demonstrating a consistent change from baseline following DMP 115.

The data demonstrates that DMP 115 may assist in determining endocardial border delineation and length.

Studies 006 and 007 proved a statistically significant gain in the measurement of the endocardial border following the administration of DMP 115. Study DMP 115-004 supports the claim for endocardial border delineation although study 005 does not. Both claims are nearly identical and mutually supportive of a claim for delineation of the endocardial border.

DMP 115 showed a statistically supported improvement, for fundamental echocardiography to assess wall motion however, this is a qualitative evaluation that lacks support as MRI is not a proven standard.

Recommendations:

Cardiac safety has not been adequately tested. ECG safety data, closer to the time following dose administration, will better evaluate cardiac safety. Studies of end-systolic triggered imaging at high acoustic power (mechanical index >1.0) should be conducted.

The studies restricted enrollment of patients with serious COPD and/or CHF. Patients with pulmonary hypertension should be studied to evaluate the safety profile of DMP 115. Oxygen saturation and ECG data is of concern in these patients.

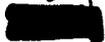
Evidence for dose repetition is needed. At present the 10 μ L/kg may be repeated once.

DMP 115 is approvable for ventricular cavity enhancement and endocardial border delineation/measurement.

1S/0
-M.D. 7/26/99
A. Eric Jones M. D.
Clinical Team Leader, HFD-160

CC: NDA 21-064

Division File

Project Manager: *Nguyen* 

Division of Medical Imaging and Radiopharmaceutical Drug Products: HFD-160

NDA 21-064

Definity (DMP-115/Perflutren Lipid Microspheres)

Response to Action Letter of August 4, 2000

Du Pont Pharmaceuticals

331 Treble Cove Road

North Billerica MA 01862

Submitted: January 30, 2001

Review Date: May 17, 2001

Clinical Team Leader's Review

Summary:

Two prior NDA submissions for Definity resulted in action letters that were issued October 8, 1999 and August 4, 2000 noting that there

The surrogate endpoints of left ventricular (LV) opacification and improved delineation of the LV endocardial border (LVEB) were historically assumed to support echopharmaceutical cardiac function claims, i.e., to improve the assessment of LV wall motion. Du Pont did not submit data to test the validity of the assumption of the clinical usefulness of these surrogate endpoints to provide a LV function efficacy claim for Definity. The most recent action letter August 4, 2000, asked Du Pont to provide additional documentation that the surrogate endpoints have clinical usefulness by examining regional as well as segmental changes in cardiac wall motion.

The present submission of NDA 21-061 on January 31, 2001, contains a re-analysis of original data from studies DMP 115-006 and DMP 115-007 intended to validate the surrogate endpoint LVEB. It also provides a response to other issues raised in the August 4, 2000 action letter that are addressed in the medical officer's review.

The clinical and statistical reviews suggest that Definity may convert non-evaluable cardiac wall segments allowing identification of normal wall motion but would not improve the detection of abnormal LV wall motion seen prior to the use of Definity.

This secondary review recommends that the Clinical Trials section of the proposed label contain wording that the data suggests an improvement in the detection of normal LV wall motion that may support the validity of the use of the surrogate endpoints: LV opacification and improved visibility of LVEB. The indication should be limited to claim: "Definity is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders".

Review:

Both the statistical and clinical reviews noted that the segmental and regional wall motion results of studies -006 and -007 were not in agreement. The statistical analysis of study -006 indicated an adequate level of agreement between MRI and post-Definity improvement in the assessment of segmental and regional cardiac wall motion. This was not replicated in study -007 where a majority of images indicated that there was no statistical difference in pre- and post-Definity LV wall motion.

The clinical and statistics reviews noted that study -006 enrolled normal patients for the most part, 44/61 (72%) and study -007 had a majority of patients who were abnormal 44/57 (77%). The effect of this patient mix on the efficacy outcome was evaluated by asking the sponsor to compare the pre- and post-Definity segmental results for normal and abnormal patients enrolled in each study.

The truth standard for judging normal and abnormal segmental cardiac wall motion was the MRI study result for each patient. In both studies, -006 and -007, the post-Definity images correctly identified more MRI-normal patients than abnormal patients compared to pre-Definity. For patients with MRI-abnormal wall motion the comparison indicated no improvement in the post-Definity images over the pre-Definity images. Definity may improve the ultrasonographer's ability to identify normal LV wall motion for patients where the pre-Definity ultrasound images are equivocal.

This analysis may explain why study -007, consisting of mostly abnormal patients, failed to show a statistically significant difference in regional and segmental wall motion between pre- and post-Definity images.

The reason for the enrollment difference, in the MRI designated normal and abnormal patients between studies -006 and -007, is unknown to the reviewers. The inclusion and exclusion criteria are identical for both studies. A range of disease severity was included in both studies and NYHA Class IV cardiac patients were excluded.

Conclusion:

I agree with the Medical Officer's review that the sponsor has been unable to demonstrate adequate evidence to support a claim to be able to assess cardiac function. Definity was not shown to improve echocardiographic detection of abnormal wall motion in either of the two trials DMP 115-006 or 007. It improved the detection of normal wall motion in study DMP 115-006.

Recommendation:

Approval with the indication limited to the claim:

DRAFT

The Clinical Trials section of the labeling should reflect that the LVEB claim contains limited evidence to support the assessment of myocardial wall motion.

Labeling:

Place the following in the Clinical Trials section of the labeling:

DRAFT LABELING

Also:

The following statement should be added at the end of the Clinical Trials section of the label. It is found in current approved ultrasound drug labeling.

DRAFT LABELING

/s/

A. Eric Jones MD
Clinical Team Leader, HFD-160

CONSULTATION RESPONSE

**Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)**

DATE RECEIVED: 8/ 8/ 2000

DUE DATE: 11/ 17/ 2000

OPDRA CONSULT #: 00-0219

TO:

Patricia Love, M.D.
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
(HFD-160)

THROUGH:

Thuy Nguyen
Project Manager
(HFD-160)

PRODUCT NAMES:

Definity (Perflutren Lipid Microsphere Injectable Suspension)

MANUFACTURER: DuPont
Pharmaceutical Company

NDA #: 21-064

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:

From a safety perspective, OPDRA has no objections to the use of the proprietary name, Definity.

- FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW**
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.
- FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW**
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.
- FOR PRIORITY 6 MONTH REVIEWS**
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

J.P. 1/27/00
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

M.S. 11/27/00
Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Cho

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 21, 1998
FROM: Kaye Cho, Pharm.D.
SUBJECT: LNC Consult []
TO: Original IND [] Division File

The following information is in regards to the sponsor's proposed name for their drug product - DMP-115 (IND []) Du Pont is expected to submit an NDA in December of 1998, and in the process, the sponsor has asked to evaluate their proposed tradename [] A consult was requested to the Labeling and Nomenclature Committee and the result of the consult is attached to this memo.

cc:
Original IND []
HFD-160/Div. Files
HFD-160/Cho/Kasliwal

REQUEST FOR TRADEMARK REVIEW

COPY

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Medical Imaging and Radiopharmaceutical Drug Product	HFD-160
Attention: Ravindra K. Kasliwal, Ph.D.	Phone: (301)827-6318
Date: 6/18/98	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: [. . .]	IND#: []
<p>Established name, including dosage form: The drug product is composed of a lipid blend (mixture of 3 lipids) and perfluoropropane gas in a matrix of 0.9% sodium chloride, propylene glycol and glycerol in water for injection. Upon shaking in a dental amalgamator, it provides perfluoropropane filled, lipid encapsulated microbubbles (the active moiety responsible for contrast enhancement). Prior to shaking contents appear translucent. Upon shaking , the contents appear as milky white suspension. In my opinion the dosage form, in this case, will be "Injectable Emulsion". No established name yet.</p>	
<p>Other trademarks by the same firm for companion products: The sponsor does not have any other ultrasound drugs. (there are only two other approved ultrasound agents on the market, OPTISON and ALBUNEX)</p>	
<p>Indications for Use (may be a summary if proposed statement is lengthy): Potential indications (none approved yet) for contrast enhancement during ultrasound study may include :</p>	
<p>Initial Comments from the submitter (concerns, observations, etc.): The sponsor would like to find out whether this name would be acceptable when the NDA is submitted.</p>	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Division File IND []

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE REVIEWED: November 13, 2000
NDA#: 21-064
NAME OF DRUG: Definity (Perflutren Lipid Microsphere Injectable Suspension)
NDA HOLDER: DuPont Pharmaceutical Company

I. INTRODUCTION:

This consult is in response to an August 8, 2000 request, by the Division of Medical Imaging and Radiopharmaceutical Drug Products, to review the proposed proprietary drug name, Definity, regarding potential name confusion with other proprietary/generic drug names. The container label, carton labeling, and the package insert were also submitted for review of possible interventions in minimizing medication errors.

The proposed proprietary name, Definity, was previously reviewed by the Labeling and Nomenclature Committee (LNC) in September 1998 and was found to be acceptable. On the basis of LNC's review, the applicant was told that the name, Definity, was acceptable. The applicant received an *approvable* letter on August 4, 2000 (PDUFA 8/8/00)

PRODUCT INFORMATION

Definity is a diagnostic agent that is intended to be used for contrast enhancement during the indicated ultrasound imaging procedures. When activated with the aid of Vialmix, it yields perflutren lipid microspheres, which are composed of octafluoropropane encapsulated in an outer lipid shell. Vialmix apparatus is available from Dupont Pharmaceuticals Company. Activated Definity is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The recommended dose for activated Definity is a single dose of 10 microliters/kg of the activated product by intravenous bolus injection over 30-60 seconds, followed by a 10 mL saline flush. If necessary, a second 10 microliters/kg dose may be administered 30 minutes after the first injection. Definity is supplied in single use 2 mL vials.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound-alike or look-

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

alike Definity to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted prescription analysis studies consisting of written prescription studies and a verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An expert panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, Definity. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of OPDRA medication errors prevention staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel did not identify any significant sound-alike and/or look-alike proprietary names that were thought to have potential for confusion with Definity. The consensus was that the proposed proprietary name does not pose a safety risk due to name confusion.
2. According to DDMAC, the proposed proprietary name is fanciful and promotional in tone. Also, the proposed name encodes its indication in the name, which affects the DDMAC's ability to enforce reminder ads. Therefore, Definity is objectionable in accordance with 21 CFR 202.1 (e)(2)(i), 201.100 (f), 201.56 (b), and 201.10 (c)(3).

PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

The studies conducted by OPDRA involved 90 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Definity with other drug names due to the similarity in handwriting and verbal pronunciation of the names. Written prescriptions, consisting of (known/unknown) drug products and a prescription for Definity were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, verbal orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving the prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

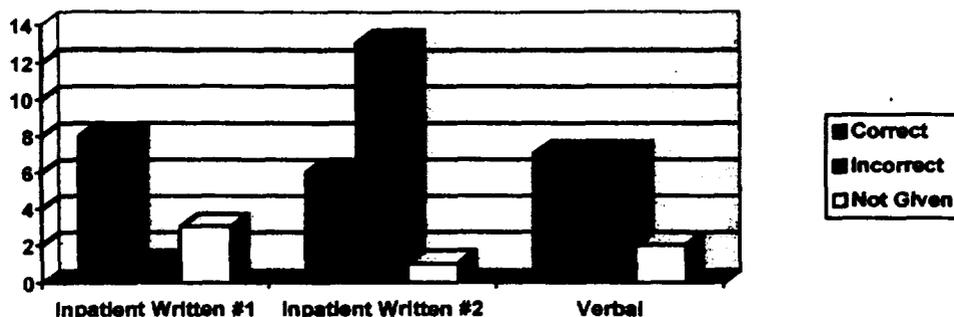
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
<i>Inpatient #1: Definity 70 uL IV over 60 seconds, follow with 10 mL NS flush</i>	<i>Inpatient: Definity 70 uL IV over 60 seconds, follow with 10 mL NS flush</i>
<i>Inpatient #2: Definity 70 uL IV over 60 seconds, follow with 10 cc NS flush</i>	

⁴ Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

2. Results:

Study	# of Participants	# of Responses	"Definity" Response	Other Responses	No Response
Inpatient Written #1	31	12 (38.7 %)	8 (66.7 %)	1 (8.3 %)	3 (25 %)
Inpatient Written #2	30	20 (66.7 %)	6 (30 %)	13 (65 %)	1 (5 %)
Verbal	29	16 (55.2 %)	7 (43.75 %)	7 (43.75 %)	2 (12.5 %)
Total	90	48 (53.3 %)	21 (43.75 %)	21 (43.75 %)	6 (12.5 %)



Since Definity is a diagnostic agent and would not be dispensed in an outpatient setting, two written studies, which normally consist of inpatient and outpatient prescriptions, were conducted with only inpatient prescriptions. Both studies consisted of the same drug order, but two different handwriting samples were utilized.

Among participants in the two written prescription studies for Definity, fourteen (43.8 %) out of thirty-two study participants interpreted the name incorrectly. According to the *inpatient written study #1* results, one study participant interpreted the name as *Definilz*. According to the *inpatient written study #2* results, ten (10) study participants interpreted the name as *Difinity*. Other interpretations include *Afinity* (2) and *Divinity* (1). In these two studies, most of the incorrect name interpretations were misspelled variations of the proprietary name, and the responses did not overlap with existing proprietary names.

Among the verbal prescription study for Definity, seven out of sixteen (43.75 %) participants interpreted the name incorrectly. Three (3) study participants interpreted the name as *Difinity*. Also, there were two (2) interpretations for *Difnidine*. Other interpretations include *Definitie* and *Tefenati*. Similar to the written studies, the incorrect name interpretations were phonetic variations of the proprietary name, and the responses did not overlap with existing proprietary names.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. According to DDMAC, the proposed proprietary name, Definity, is fanciful and promotional in tone, and therefore, objectionable in accordance with 21 CFR 201.56 (b) and 201.10 (c)(3). Furthermore, the proposed name encodes its indication in the name, which affects the DDMAC's ability to enforce reminder ads. Therefore, Definity is also objectionable in accordance with 21 CFR 202.1 (e)(2)(i) and 201.100 (f).
2. According to our searches, the proposed proprietary name, Definity, does not have the potential for name confusion with existing product names and poses no significant safety risk. We also conducted both written and verbal studies, which simulate the prescription ordering process, in order to detect potential medication errors. However, these studies did not result in any significant look-alike or sound-alike product names.

The majority of the participants in the *inpatient written study #1* misinterpreted the proposed proprietary name. However, the majority of the participants in the *inpatient written study #2* interpreted the proposed name correctly. The results were evenly split in the *verbal* study. In these studies, it is noteworthy that many incorrect interpretations were misspelled/phonetic variations of the drug name, and the interpretations did not overlap with existing proprietary and established names. Furthermore, although we recognize that there are limitations to the predictive value of these studies, primarily due to their sample sizes, the results of these studies confirm the findings expressed by the expert panel discussion.

Although DDMAC's objections are noted, given the above findings, OPDRA has no objections to the use of the proprietary name, Definity, from a safety perspective.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, carton labeling, and the package insert for Definity, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. The current labeling does not indicate the *strength* of the product and the *total volume* that is contained in each vial. We recommend adding this information to the front of the label.
2. The current label reads, "Store at 2-8°C, use within 12 hours of activation." This statement is misleading since the **activated** drug should be stored at room temperature and may be used for up to 12 hours from the time of activation. The **inactivated** drug is to be stored in the refrigerator. We suggest clarifying these storage recommendations.
3. The bar code-like design next to proprietary name is distracting to the eye and detracts attention away from the proprietary name. We recommend deleting this design. We recommend the following presentation of the name:
 4. *If space permits*, we recommend adding the following statement:
 5. *If space permits*, we recommend adding the following statement:
6. The NDC number must be preceded by "N" or "NDC" and appear in the upper 1/3 of the principle display panel.

B. CARTON LABELING

1. On the side panel of the carton, the storage information, the statement of ingredients in each vial, and the contents of the carton are all combined in the labeling, and therefore, confusing to the user. We recommend the following revisions:

- a. Relocate the *contents of the carton*, “1 package insert and 4 vials”, to the main panel. In addition, since a package insert is always provided with the drug, we recommend revising the above statement to read as follows:
 - b. Separate the statement of ingredients and the storage information by revising the “CONTENTS AND STORAGE CONDITION...” statement. In regard to the *statement of ingredients*, the labeling should clarify which ingredient is available in the vial before and after activation.
 - c. According to the statement of ingredients, the *activated* suspension contains 1.2×10^{10} perflutren lipid microspheres. We recommend that the *amount* of perflutren lipid microspheres in each mL be presented in terms of its mass (e.g. micrograms) in addition to the number of microspheres.
2. On the main panel of the carton, we recommend decreasing the prominence of the manufacturer and distributor information so that other essential information such as the *strength* and the *contents of the cartons* could be expressed prominently on the main panel.
 3. In addition, we recommend relocating the “Rx Only” statement and “For Intravenous Administration, After Activation” statement to the main panel.
 4. The statement, “Not for direct administration,” is misleading since the proposed drug is to be given via direct IV bolus administration. We recommend deleting this statement.
 5. Since the proposed drug is *clear* before activation and *cloudy* after activation, this conversion should be addressed in the carton labeling so that the user is aware of the change and would not be confused about administering a cloudy substance intravenously.
 6. See comments under CONTAINER LABEL.

C. PACKAGE INSERT

1. Under DOSAGE AND ADMINISTRATION section, the labeling states that “*the microspheres must be resuspended by 10 seconds of hand agitation...*” This direction is not clear since the vial could be gently rolled or shaken depending on the interpretation. We recommend specifying the exact method for resuspending the suspension.
2. Under DOSAGE AND ADMINISTRATION section, we recommend revising the expression of the dose, “10 μ L/kg” to read, “10 microliters/kg”. Based on our post-marketing experience, the symbol “ μ ” could resemble “m” in a prescription.

IV. RECOMMENDATIONS:

- A. From a safety perspective, OPDRA has no objections to the use of the proprietary name, Definity.
- B. OPDRA recommends the above labeling revisions that might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the vision for further discussion, if needed. If you have further questions or need clarifications, please contact Lammie Beam at 301-827-3161.

Memo

To: Patricia Love, M.D.
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

From: Jerry Phillips, R.Ph.
Associate Director, Office of Post-Marketing Drug Risk Assessment
HFD-400

CC: Thuy Nguyen
Project Manager
HFD-160

Date: June 1, 2001

Re: OPDRA Consult 01-0106; Definity (Perflutren Lipid Microsphere Injectable Suspension);
NDA 21-064

This memorandum is in response to a May 16, 2001, request from your Division for a re-review of the proprietary name, Definity.

OPDRA has not identified any additional proprietary or established names that have the potential for confusion with Definity since we conducted our initial review on November 13, 2000 (OPDRA consult 00-0219), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

However, DDMAC has found the name objectionable from an advertising and promotion perspective. According to DDMAC, the proposed proprietary name is fanciful and promotional in tone. In addition, the proposed name encodes its indication in the name, which affects the DDMAC's ability to enforce reminder ads. Therefore, Definity is objectionable in accordance with 21 CFR 202.1 (e)(2)(i), 201.100 (f), 201.56 (b), and 201.10 (c)(3).

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3231.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Deputy Division Director Memorandum to the File

NDA: 21,064
DRUG: Definity vial (for perflutren lipid microspheres) injectable suspension
ROUTE: Intravenous
MODALITY: Ultrasound Contrast
INDICATION: Endocardial Border Delineation (EBD),
Left Ventricular Opacification (LVO)
CATEGORY: IS
SPONSOR: Dupont Pharmaceutical Co.
SUBMITTED: January 31, 2001
PDUFA DATE: July 31, 2001
COMPLETED: July 4, 2001
RELATED DRUGS: Optison (Albumin human 1% with perfluoropropane microspheres) NDA 20,899 approved for EBD and LVO
Albunex (Albumin human 5% sonicated) PMA

REVIEW TEAM:

Chemistry: R. Kasiliwal PhD 9/09/99, 07/27/00
Clinical: J. Zolman, MD 09/02/99, 07/20/00
Clinical Pharmacology: D. Lee, PhD 08/23/99, 07/26/00
Division Summary: PY Love, MD 10/09/99, 07/31/00
S Loewke 7/10/01
Microbiology: B. Riley, 04/05/99
Pharmacology/Toxicology: A Laniyonu, PhD, 08/16/99, 06/06/00
N Sadrieh, PhD 08/16/99
Statistics: M Sovhan, PhD, 06/18/99, 07/06/00
Project Manager: T Nguyen, MPH

BACKGROUND:

Definity vial for the preparation of perflutren lipid microspheres injectable suspension, manufactured by DuPont Merck Pharmaceutical Company, is resubmitted for evaluation of its safety and efficacy in providing ultrasound contrast enhancement in echocardiography. Definity was originally submitted on December 09, 1998 and resubmitted on February 08, 2000. Both submissions resulted in Approvable letters dated October 09, 1999 and August 04, 2000 respectively. The most recent Approvable letter cited the following unresolved issues:

Safety Related:

- 1.) Ongoing deficiency to provide sufficient manufacturing controls for microsphere upper size limit
- 2.) Ongoing deficiency to provide animal studies in a chronically compromised pulmonary model and a microvascular study (intra-arterial injection)

Efficacy Related:

- 3.) Ongoing deficiency to validate wall motion endpoint
- 4.)

The Sponsor has adequately addressed the above deficiencies and Definity is recommended for Approval.

This memo will address each of the above deficiencies in the same order as listed above. Specifics of the deficiency will be presented first followed by the resolution or outstanding issues.

- 1.) Ongoing deficiency to provide sufficient manufacturing controls for microsphere upper size limit to ensure safety of the administered product

The last review cycle revealed that the maximum concentration of microspheres in the suspension is 1.2×10^{10} microspheres/mL with a Sponsor proposed limit where 0.2% of the microspheres potentially being larger than 20 μm (largest 47 μm). This 0.2% limit could potentially result in up to 2.4×10^7 microspheres in the large size range thus increasing the risk of embolic potential in susceptible patients. Therefore, elimination of the larger microspheres from the injectate was recommended in the Approvable letter (8/4/2000).

The original method of size distribution validation was the AccuSizer method which identified particles larger than 20 μm , however, this was thought to be an artifact due to coincidence counting. In order to validate this assumption, the Sponsor performed stereo (optical) microscopy, which confirmed the upper limit of microspheres as being 20 μm . Dr. Kasliwal finds this methodology and the limits set below as acceptable.

Mean Microsphere Diameter: 1-3.3 μm
Percent Microspheres, $1\mu\text{m} \leq \text{diameter} < 6\mu\text{m}$: NLT 90%
Percent Microspheres, $1\mu\text{m} \leq \text{diameter} < 10\mu\text{m}$: NLT 98%
Percent Microspheres, $1\mu\text{m} \leq \text{diameter} < 20\mu\text{m}$: NLT 99.8%
Total Concentration: 6.0×10^7 to 1.2×10^{10} microspheres/mL

As per Dr. Kasliwal's review, the Sponsor's justification for not using a was found acceptable. The overall findings were that

These results did not justify the use and could potentially lead to alteration of the product if used.

Overall Dr. Kasliwal finds that the Sponsor has demonstrated adequate control over the manufacture of the proposed drug product and can reproducibly manufacture the drug product of defined identify, strength, quality and purity. I agree with Dr. Kasliwal's assessment.

2.) Ongoing deficiency to provide animal studies in a chronically compromised pulmonary model and a microvascular study (intra-arterial injection)

The previous capillary study was performed on an intravenous model (cremasteric muscle) and did not identify any obstructive effects by Definity. This model was not found to be acceptable as it studied the effects of Definity after it had been filtered by the lungs. It was, therefore, requested that an intra-arterial injection be studied to more closely model the effects that might occur in patients with cardiac shunting. The study performed utilized an intravital microscopic study of the Sprague-Dawley rat spinotrapezius muscle at doses up to 6 times the maximal human dose. Results identified the presence of microsphere-induced vascular obstruction occurring with microspheres $> 5 \mu\text{m}$. This obstruction was noted at 1 minute with significant reduction in obstruction potential by 10 minutes post administration. Static microspheres were seen in small arterioles $< 15 \mu\text{m}$ especially at branch points and in capillaries. Mean blood flow in larger diameter arterioles (18-30 μm) was not altered. There was no evidence of microsphere coalescence or growth in size, however entrapped microspheres did deform to an ellipsoid shape allowing for passage through the microvasculature. The Sponsor attempted to extrapolate this data to humans, however as Dr. Lanianyu states, this type of extrapolation relies on too many assumptions that make it difficult to draw any conclusions about the potential safety in humans. Dr. Lanianyu suggests that this finding be discussed in labeling, in particular, citing a warning about the use in patients with cardiac shunts. I agree with his assessment.

The other study requested was one in a chronically compromised pulmonary model. The sponsor, however, performed a cardiovascular study in an acute pulmonary hypertensive model in a closed-chest, anesthetized dog at increasing doses up to 5 times the maximal human dose. This model was accomplished by the injection of Sephadex beads to simulate acute obstruction. The findings of this study do not suggest any significant impact of Definity administration on mean arterial pressure, myocardial contractility, respiration rate, and QTc when compared to a control. This acute model does not evaluate the effect of the drug on a narrowed and decreased vascular bed with little reserve (e.g. patient with chronic pulmonary hypertension). Therefore this acute model cannot suffice for a chronic model. However, since an appropriate chronic animal model has yet to be developed, this acute model provides some useful information. Therefore, appropriate warnings are needed in labeling for use in patients with chronic pulmonary compromise.

Dr. Lanianyu proposes that the Sponsor study the fate of the intact or degassed lipid microsphere and the potential effects of the drug-device interactions on endothelial integrity as Phase 4 commitments. Since the Sponsor has only studied the fate of the gas and since there is evidence with other drugs of this class that there may be gas exchange in vivo, I agree with the suggestion for a Phase 4 commitment to study the fate of the microsphere.

With regard to the drug-device concern, labeling will include the device mechanical index settings used in the clinical trials. Since there is no evidence to suggest that use within this range poses significant risk, the sponsor should be advised to investigate this scientific phenomenon if they plan to use mechanical indices (MI) above those that will be specified in labeling. Also, if under the IND, Definity is studied for other cardiac indications or in other areas of the body, additional MI data are needed.

3.) Ongoing deficiency to validate wall motion endpoint

A microsphere contrast agent (Albunex) was originally approved by the Center for Drugs and Radiologic Health (CDRH) with the following endpoints, left ventricular opacification and endocardial border delineation. These endpoints were thought to act as surrogates for the more clinically meaningful endpoints of wall motion and ejection fraction. In 1997 in response to a citizen's petition, the FDA announced that all ultrasound contrast agents would be regulated by Center for Drug Evaluation and Research (CDER). The first CDER approval was in 1997 for LVO and EBD (Optison®). Since this approval many Sponsors have studied, as part of their development plan, the more relevant functional endpoints as secondary in conjunction with the primary endpoints of LVO and EBD. Recently, it has been found, as in the case with Definity, that the noted improvement in LVO and EBD was not translating into improvement in the clinically relevant functional endpoints (e.g.

wall motion). Whether this lack of improvement is because of the trial design or is an inherent deficiency in the drug class could not be determined from the existing data. Therefore, DuPont and other Sponsors have been asked to address this issue and at a minimum identify functional trend data in addition to their primary anatomic endpoint data to provide a basis for the drug's clinical utility. This trend data would than suffice to support approval of the anatomic endpoints. This approach to Approval is being utilized here as a means to transition those drug products, that in good faith, studied the anatomic endpoints as their primary efficacy endpoint under the original assumption that they would act as a surrogate for the more clinically relevant endpoints of cardiac function. It is expected that all new products under development, as well as those products still in early development, study the more relevant primary endpoints of function in a manner that is consistent with their clinical use (e.g. reproducibility in an outpatient setting).

Briefly, DuPont has studied Definity for both cardiac anatomic and functional endpoints. To date, the submission has provided adequate data to support the LVO and EBD claims (See Dr. Love's review of 10/09/99 for details).

requested that the Sponsor address the inconsistencies in the wall motion data, as evidenced in the previous review cycle as mean differences (from baseline) in segmental wall motion ranging from 22-41% (depending on reader) for study 006 compared to 1-30% for study 007 (as Per Dr. Loves review date 10/09/99).