

However, in continued attempts to show support for the wall motion claim, the Sponsor has resubmitted a different reanalysis of their original data despite the request for either additional study data or literature data. This reanalysis used a condensed wall motion rating scale (non-evaluable, normal and abnormal) with comparison to a subset of patients with MRI as the gold standard. (NOTE: As identified in Dr. Loves review dated 7/31/00, results from blinded reader #5 were not considered independent and thus will not be considered for any of the following presented analyses.)

Review of this current reanalysis has resulted in both the clinical (Dr. Zolman) and statistical (Dr. Sobhan) reviewers recommending an Approvable action based on the continued inconsistency in the magnitude of improvement for wall motion across studies 006 and 007. In attempts to address the inconsistency, Dr. Zolman has identified what appears to be a difference in patient populations between studies 006 and 007 despite the fact that the same protocol was followed. Retrospectively, study 006 appears to have a larger non-diseased population, with 77 % of the population having normal wall motion as determined by MRI vs. 23% normal wall motion in study 007. After identifying this difference, a further analysis, based on patient population classification of "normality" or "abnormality", was requested from DuPont. The results of this patient-level analysis (Table 1) show that there is better agreement between MRI and post-Definity when compared to the baseline image for defining normal wall motion versus abnormal wall motion. Segmental analysis (attached Appendix A) shows a statistically significant difference between baseline and post Definity agreement with MRI for all segments for 2 out of 4 blinded readers. Based on the trend in patient-level wall motion results, the clinical teamleader (Dr. Jones) recommends Approval for the endocardial border and left ventricular opacification claims.

However, the data suggesting that Definity improves the detection of normal wall motion, in his opinion, would suffice to support the validity of the clinical utility of the anatomic endpoints with specific labeling restrictions.

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The wall motion concordance with MRI for these converted images by the "normal" and "abnormal" patient population category is listed in Table 4. Overall, the percent match with MRI for abnormal wall motion was between 67-83% for three out of the four readers. The percent match for normal wall motion was in a similar range for 2 out of the 4 readers (67 and 69%). Overall the sample sizes are small and this exploratory analysis does not support any statistical significance to these findings. These findings may, however, offer enough of a trend to support the anatomic endpoints with restricted labeling.

TABLE 4. MRI Concordance When 2 Adjacent Segments Read as Non-evaluable for Wall Motion at Baseline Convert (at least one out of the two segments) to Evaluable post-Definity

	Normal		Abnormal		Overall	
	N	% MRI Match*	N	% MRI Match*	N	%MRI Match*
Study 006						
Reader #1	26	69%	12	67%	38	68%
Reader #2	27	30%	11	73%	38	42%
Study 007						
Reader #3	1	0%	6	83%	7	71%
Reader #4	9	67%	22	46%	31	52%

Reference: Submission dated 6/29/01, page 2. * Percent wall motion match between post-Definity and MRI.

One additional analysis was requested that looked at the wall motion concordance with MRI with increasing numbers of segments rated as non-evaluable at baseline. No trends could be identified from this analysis.

Additional Issues not present in the Action Letter:

1.) Safety Update: Reviewed by Dr. Zolman

The data are similar to that provided in the original submission and are included in labeling. In his previous reviews and in his current review, Dr. Zolman continues to express concern about the lack of ECG data collected within the first hour post-Definity administration. This period is particularly relevant given what is known about the kinetics of this drug and the potential drug-device interactions seen with other drugs of this class (i.e., premature ventricular contractions seen with high mechanical indices). Therefore, the Sponsor should address the ECG safety of Definity within the timeframe immediately post-dosing as part of any future or on-going IND studies, as these studies may use high mechanical indices.

2.) Pediatrics:

The Sponsor submitted a deferral request for children and a partial waiver request in neonates. On January 22, 2001 the Agency issued a letter granting the Sponsor a deferral for all pediatric age ranges. The Sponsor has since submitted a request for exclusivity (April 3, 2001) with a proposed pediatric study timeline only. The Sponsor was notified in a telephone conference that a proposed pediatric study request will need to be submitted for review an issuance of a written request. The Sponsor will be formally notified in the action letter that they must submit a proposed pediatric study request (PPSR) and receive a written request from the Agency in order to be eligible for exclusivity.

ASSESSMENT:

Definity has previously shown adequate data to support the EBD and LVO indications. This submission shows that Definity was able to convert a baseline non-evaluatable wall motion image (as defined as 2 non-evaluatable segments) to an evaluatable image. This is consistent with the current clinical guidelines for the use of contrast echocardiography. Of those patients whose images had been converted to evaluatable by Definity, the concordance with MRI for wall motion was variable across readers but thought to be within the range of that for the non-contrast modality in an evaluatable population. Therefore, this submission has provided sufficient transitional data to support the potential clinical utility of the anatomic endpoints in patients who have at least 2 segments non-evaluatable on baseline (non-contrast) echocardiography.

ACTION: Approval

Labeling should include:

- 1.) The statement that Definity is to be used in patients with 2 or more non-evaluatable segments on a non-contrast echocardiograms as part of the indication.
- 2.) A statement about the potential for Definity to obscure the image thus non-contrast and contrast images should be evaluated together.
- 3.) A statement about the vascular obstruction potential seen in pre-clinical studies (intra-arterial)
- 4.) A statement about the range of mechanical indices used in the clinical trials.

Phase 4 Commitments:

- 1.) Pre-clinical studies addressing the length of persistence and fate of the microsphere in vivo. These studies should address the potential for microsphere gas exchange in vivo.

- 2.) Completion of preclinical studies of the effects of mechanical ventilation on the microsphere characteristics and the toxicity of Definity. Pending results, additional studies in humans may be needed.
- 3.) Adverse event surveillance study.

NOTE: Sponsor concurrence of final labeling was obtained on July 30, 2001.

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DIVISION DIRECTOR MEMORANDUM TO THE FILE

NDA: 21,064
DRUG: Definity Kit for the Preparation of Perflutren Lipid Microspheres Injectable Suspension
USAN: Perflutren Lipid Microspheres
CLASS: Echopharmaceutical ("microaerosomes" or "microbubbles")
ROUTE: Intravenous
MODALITY: Ultrasound
INDICATION: Cardiac } Ultrasound Contrast Enhancement (Proposed)
SPONSOR: DuPont Merck Pharmaceutical Company
SUBMITTED: 12/09/98
FDUFA DATE: 10/09/98
COMPLETED:

RELATED DRUGS:

Optison (Albumin human 1% with perfluoropane microbubbles); NDA #20899; approved
Albunex (Albumin human 5% sonicated); PMA approved
Multiple INDs ongoing;

RELATED REVIEWS:

Chemistry - R. Kasliwal, Ph.D., 9/9/99
Clinical - J. Zolman, M.D., Ph.D. 9/02/99
Clinical Pharmacology - D. Lee, Ph.D. 8/23/99
Microbiology - B. Riley, Ph.D., 04/05/99
Pharmacology-toxicology - A Laniyonu, Ph.D, 8/16/99; N. Sadrieh, Ph.D. 8/16/99
Statistics - M. Sobhan, Ph.D., 06/18/99
Project Manager - Kyong Cho, Ph.D.

BACKGROUND

Definity Kit for the Preparation of Perflutren Lipid Microspheres Injectable Suspension is manufactured by DuPont Pharmaceutical Company and is submitted for proposed uses in ultrasound contrast enhancement in echocardiography. Definity is one of a new class of imaging contrast agents known as either echopharmaceuticals, microspheres, microaerosomes, or microbubbles. These are gas filled flexible particles that provide acoustic enhancements when exposed to ultrasound waves. During the early development, Definity was initially owned by ImRx Pharmaceutical Corporation and was termed MRX 115. After DuPont assumed the development, the drug became known as DMP 115.

The Definity NDA contains proposed diagnostic contrast enhancement indications: one in cardiac ultrasound. The NDA review is complete and is found to be acceptable for an approvable action with additional information needed to resolve outstanding safety issues that affect chemistry, clinical and pharmacology; and clarifications in the clinical pharmacology section. The key issues will be addressed in this memorandum.

CHEMISTRY

Definity Kit for the preparation of perflutren lipid microspheres injectable suspension is supplied as a vial containing a clear, colorless, sterile, liquid that is activated by an automated device to produce a homogenous, opaque suspension of microspheres. The contents of the vial include three different lipids:

- (abbreviated DPPA);
- DPPC); and
- (abbreviated MPEG 5000 DPPE).

After activation, these 3 lipids form the microsphere outer shell. During the course of drug development three different methods were used to mix the lipids. However, as per Dr. Kasliwal, evolution of the mixing process resulted in the same or an improved end product. The gas within the microsphere is octafluoropropane (also known as perfluoropropane) and has a boiling point of 37°C. The vial size is 2 ml with a 1.5 fill. All vial contents are listed in table 1.

Ingredient	Concentration
Perfluoropropane	NTL % in headspace
Lipid blend of	
DPPA	0.045 mg/ml
DPPC	0.401 mg/ml
MPEG 5000 DPPE	0.304 mg/ml
Sodium chloride, USP	1 mg
Propylene glycol, USP/EP	mg
Glycerin, USP/EP	mg
Water for Injection, USP	
Sodium hydroxide, NF	Adjust pH to -7.0
Hydrochloric acid, ND	Adjust pH to - 7.0

In order to form the microbubbles an automated procedure is used that is similar to the vigorous agitation device used to mix a dental amalgam (amalgamator). It is known as a VialMix and was developed specifically to prepare the microbubbles. The VialMix is not included in the kit. It is sold separately by DuPont. Descriptions of the VialMix should be added to the package insert.

After the microspheres are formed, their concentration is approximately to 1.2×10^{10} microspheres per ml. The size and concentration appear to be stable for up to 12 hours. However, after activation and 5 minutes of sitting on the shelf, the microspheres will settle to the bottom of the vial. They should be resuspended by 10 seconds of hand shaking before injection.

During the review several questions were sent to the sponsor about the validation of the automated activation device, the particle size and concentration, the time after activation, hand resuspension, etc. The responses were reviewed by Dr. Kasliwal and are discussed in his review pages 65-73. In table 2 of this memorandum is a synthesis of his discussion and assessments that are key to the overall safety of the microbubbles. The table notes the size distribution, time after activation, susceptibility to variation in the automated activation, effects of the injection tubing and needle, time after activation, fragility, temperature, infusion media, and repeat Vial Mix agitation.

As shown in table 2, at least 95 % of the microbubbles are less than 10 μm in diameter. In earlier discussions with the sponsor it appeared that the manufacturing process might have a cap of 22 μm ; however, the maximum size of particulate matter of any source (i.e., microbubble or not) is 47 μm . Thus far quantitation of the number of such large particles has not been provided. Whether the concentration of the larger particles is consistent with USP allowances for particulate matter is not known. As will be discussed in the pharmacology section, the microbubble size needed for imaging is < 10 μm . Therefore, chemistry recommends the use [] during the injection to eliminate bubbles or particles of a larger size.

Table 2: Summary of Microbubble Assessment*

Environmental Assessment - A categorical exclusion was granted on the basis of less than 100 ppm of environmental contaminants.

EER - As of 9/9/99 all but one of the site inspections are acceptable. One of two sites that manufacturer was not acceptable. This must be acceptable or withdrawn before approval.

Chemistry Assessment: Overall, the validation of the activation procedure to prevent unexpected use is accepted by chemistry. I agree with this assessment; however, there are two other unexpected conditions of use that were not studied or described. These are the characterization of particle size and distribution if the drug is activated but not resuspended before injection. The other affects one of the proposed dosing regimens discussed in the clinical section; i.e., the infusion of Definity diluted in 0.95 saline. While the stability of Definity in saline is adequately validated, the data on the inadvertent dilution with _____ were not presented. The medical reviewers do not recommend this regimen for approval because of insufficient safety data. *However, at such time as this route is acceptable, characterization with other common diluents should be provided.*

Generally, the particle size and concentration are well documented. Dr. Kasliwal's concern is the unspecified number of particles that are above 10 μm . Specifically, the maximum particle size of 47 μm is in the range known to be associated with micro pulmonary embolism. Since the sponsor's data demonstrate that particles above 10 μm do not contribute to the efficacy of Definity, chemistry recommends the use _____ to eliminate particles above that size. *While I agree that the, may be useful, full validation of the effect on the particle size profile is needed. Depending upon the results, bridging pharmacology or other studies may be needed. Also, exploration of a sizes might be prudent. Alternatively, the sponsor could consider whether modifications in the manufacturing process could limit the production of the larger particles to USP specifications.*

Additionally, Dr. Kasliwal recommends labeling cautions on the need to use the specific Vial Mix automated device and the resuspension requirements. The inspection failure should be acceptable before approval; and clarifications and validations are requested on the drug substance related components, lipids, lipid blend, drug product, specifications, analytic methods, and container closure. While the list of needed information is lengthy, each item should be readily resolvable. I agree that *these points should be in the action letter.*

MICROBIOLOGY

The sterility assurance aspects of the application were reviewed by Dr. Bryan Riley who concluded that the data are sufficient to make the microbiology portion approvable. However, Definity is manufactured at two different facilities. There are deficiencies in the sterility assurance manufacturing process that are common to both facilities and other deficiencies that are unique to each facility. Generally these deficiencies relate to the _____ process, the _____ sterilization, and the _____ I agree that *these matters need additional clarification and should be noted in the action letter.*

PHARMACOLOGY-TOXICOLOGY

The pre-clinical pharmacology and toxicology section provided information on both the efficacy and safety of Definity to support two proposed dosing regimens. These are either 1) a 10 $\mu\text{g}/\text{kg}$ bolus of Definity over 30-60 second bolus followed by 10 ml saline flush, or 2) a 4.0 ml/minute infusion of 1.3 ml Definity diluted in 50 ml of saline. This section was reviewed by Drs. Lanionu (pharmacology-toxicology reviewer) and Sadrieh (team leader) who recommend approvable pending additional safety clarifications. I agree with their recommendation. The reviews are clear and should be read for details; however, a few salient features that relate to the chemistry issues stated above will be discussed in this memo.

A. Supportive efficacy

Data were presented on the mechanism of action; the fragility of the microbubbles; the response to harmonic and fundamental ultrasound intensities; the responses over a range of doses; the documentation of the size of the microbubbles in relation to imaging, in vitro stability testing, the dosing regimens, the detection of left ventricular opacification; and the detection of myocardial perfusion defects. Dr. Laniyonu reviewed and summarized these findings in Dr. Laniyonu's review pages 8-26

1. Microbubble size, concentration and imaging results at 5 minutes and 4 days after activation

As noted in the chemistry section data were provided to validate the stability of the microbubbles over a 4-day period. These data are shown in table 3. Based upon these data, over time both the size and the concentration decrease.

Size (µm)	5 min	4 days
1 - 2	35 x 10 ⁸	9.2 x 10 ⁸
2 - 6	3.0 x 10 ⁸	1.5 x 10 ⁸
6 - 10	5.6 x 10 ⁷	4.4 x 10 ⁷
> 10	1.6 x 10 ⁷	0.8 x 10 ⁷

* Derived from Dr. Laniyonu's review page 11

These preparations were injected into dogs for imaging to determine the degree of left ventricular opacification. Optimal opacification was defined as 25 video intensity units. The graphs on page 22 (reproduced from Dr. Laniyonu's review) show the video intensity duration for the preparations injected 5 minutes and 4 days after activation. Each preparation was given in doses of 3 µl/kg bolus, 10 µl/kg bolus, and a 30 ml/kg infusion over 2 minutes. All preparations and doses provided optimal opacification over at least 6-14 minutes.

2. Intensity and duration of different doses 5 minutes after standing

In addition to the chemistry data, imaging was also performed with Definity preparations after 45 seconds of VialMix and 5 minutes of standing. Again, three concentrations were evaluated; 3, 10 and 30 µl/kg doses. As shown in table 4 derived from Dr. Laniyonu's review, the video intensity measurements were primarily related to the concentration of microspheres and the duration of opacification was primarily related to the dose. On this basis the sponsor's studies concluded that the 10 µl/kg dose was apt to be optimal.

	3 µl/kg	10 µl/kg	30 µl/kg
Peak VI	172 ± 8	181 ± 5	184 ± 2
Time to Peak	1.75 ± 0.25	2 ± 0.6	2.5 ± 0.5
Duration	8.5 ± 0.5	10.5 ± 0.3	13.5 ± 0.5

* Derived from Dr. Laniyonu's review page 10

3. Microbubble size contribution to imaging

In another study, imaging was obtained with these concentrations given in aliquots of different size particles. The aliquots were withdrawn from the top and bottom of the activated vial. The bottom aliquot had predominantly smaller particles; i.e., those sized 1-2 μm in a concentration of 6×10^6 concentration and those sized 2-10 μm in a concentration of 3×10^6 concentration. The top aliquot that predominantly larger particles; i.e., those sized 1-2 μm were similar in concentration at 5×10^6 but those sized 2-10 μm were in a larger concentration of 150×10^6 . The results of imaging with these aliquots are reproduced on page 23 (sponsor's table reproduced from Dr. Laniyonu's review). The "T" for top fraction, the "B" refers to the bottom fraction. The T aliquot with the larger particles produced more video intensity in the fundamental mode. The B aliquot with the smaller particles produced more video intensity in the second harmonic mode.

4. Other comparisons

Dr. Laniyonu's review pages 13 - 24 also presents figures to compare the fragility after exposure to ultrasound strength, different pressures, and media (blood or saline), and duration of imaging after the bolus or infusion (p 20). In all figures the imaging video intensity units and duration are displayed. These data are adequate to provide proof of concept for cardiac ultrasound and may be reviewed for additional information.

5.

A. Supportive safety:

Safety data were provided in routine and special safety pharmacology studies. These studies were comprehensive and provided adequate data from which to develop assessments; however, Dr. Laniyonu concludes that there are residual safety concerns. Dr. Sadrieh's team leader review discussed many of the same aspects from a somewhat different perspective. Both reviews, however, reached the same conclusion on the safety deficiencies. As stated in Dr. Laniyonu's review, the key areas with outstanding deficiencies are 1) "the low multiple human dose level (MHD) at which toxicity or death occurred in these studies and the scientific and theoretical considerations for the adverse reactions observed, and 2) " the impact of the time intervention between activation and injection on [the] manifestation[s] of toxicity. These issues will be briefly summarized below and focus on three key safety evaluations: the ischemic effects as demonstrated by signs of acute pulmonary embolism, cardiovascular electrophysiologic changes, and hypersensitivity manifestations. The data from the chemistry microbubble validation demonstrates stability at least until 12 hours after activation. Therefore, the second concern listed above is resolved.

1. Cardiovascular & Pulmonary:

As noted in the chemistry section, larger microbubbles might be associated with micropulmonary embolism. If these particles pass into the systemic circulation (through a right to left cardiac shunt) or if clumping or aggregation occurs, other ischemic phenomena might be observed. Cardiovascular studies were performed to measure pulmonary artery pressure, systemic pressure and electrocardiographic changes. Elevations in the pulmonary artery pressure are considered as a potential early manifestation of micropulmonary emboli. Changes in electrophysiology could reflect a variety of causes.

As noted in the pharmacology reviews, single dose toxicity studies were completed in rates, dogs and monkeys. These demonstrated that in rat studies, the acute NOEL was 5 x MHD. In the high dose group at 80 x MHD, 6/20 rats died with 30 minutes and had dyspnea, pale bodies and prostration. The deceased rats had histologic lung changes of hyperplasia, hemorrhage, interstitial pneumonia, lymphoid hyperplasia in enlarged bronchial and mediastinal lymph nodes. In a longer 28 day repeat dose study, rats that died had similar clinical and pulmonary histopathologic signs. Dr. Sadrieh concludes that "microscopic lung changes occur at or above 0.1 ml/kg" and mortality occurs at dose multiples that are species dependent.

Dr. Laniyonu's review discusses the results of several studies in dogs and primates that evaluated doses that were less than that proposed for administration to humans; e.g., dogs 0.81 MHD, 0.073 to 5.5 MHD rabbits, and 0.08 to 1.62 MHD in monkeys. The doses produced inconsistent results. In doses below the MHD, clinically significant changes were not observed in pulmonary artery pressure, systemic pressure, heart rate, and contractility. An exception is one dog that experienced a 40 mmHg (38%) decrease in blood pressure and a 95 beat per minute (46%) decrease in heart rate. These abnormalities began to reverse in 10 minutes and returned to baseline in 45 minutes. These changes did not occur on repeat dosing 3 weeks later. In anesthetized rabbits, the maximum dose was 5 MHD and changes were not seen. In anesthetized pigs the highest dose was 0.5 MHD and produced a decrease in PAP of 16 mmHg that returned to baseline in 8 minutes. Therefore, Dr. Laniyonu concludes that because of the low dose multiple (and inconsistent findings across species) the potential for cardiovascular toxicity is not clear. Dr. Sadrieh's review emphasized that the dose multiple is too low to allow for an adequate assessment. I agree. Given the upper limit of the particle size (47 μ m), *a higher dose multiple study in a compromised pulmonary vascular model should be studied.*

The pharmacology reviews also discussed the occurrence of hepatic congestion in animals that died. They speculate about the possibility that lipids may be associated with increased macrophage activity or may affect the hepatic circulation and Kupffer cell activity. Alternatively, the pulmonary congestion might be extensive enough to affect the liver. Dr. Zolman's medical review raises the question of fat embolism syndrome. However, at this time there are insufficient data to determine whether the congestion are due to fat embolism syndrome as opposed to occlusion on the basis of the size or number of microbubbles (regardless of composition).

Electrocardiographic changes were evaluated in the same studies that were used to evaluate the pulmonary artery pressures. Therefore, all minimal changes were noted, the dose multiples were too low. In two toxicology studies at higher doses in primate animals revealed ECG changes. These are one monkey upon repeat doses at 162 x MHD had ECG increased QRS, inverted T waves, and b) three monkeys after a single dose of 48 x MHD had STT depression, ventricular tachycardia, and various bundle branch blocks. The latter monkeys were given oxygen for 3-6 minutes. In discussion with Dr. Sadrieh, it appears that the toxicology studies were not designed to rigorously evaluate the ECGs. Therefore, the data were not considered conclusive.

Hypersensitivity studies were conducted in a guinea pig model. This revealed retching, head shaking, staggering, pawing nose, hyperactivity, dyspnea and negative histology. In dogs 7 day repeat dose studies, anaphylactoid responses were noted on day 4. In an antigenic study that measured histamine dose responses was positive and revealed a decrease in platelet counts; speculatively this may be secondary to a histamine release. However, in monkeys histamine and complement were not increased. According to Dr. Laniyonu, these studies suggest a mild to moderate hypersensitivity component to the acute toxicity symptoms. However, mediator release alone may not be responsible for the acute deaths noted in the single and multiple dose studies.

Other concerns about any product that must be activated or require other adjustment before injection is the toxicity of the non-activated product. Definity was tested with direct injection into animals and was not associated with death. Injection of the activated but not resuspended product was not performed. *The latter should be completed.*

Dr. Sadrieh notes that immature animals were not studied. These should be included in the sponsor's plans for developing pediatric labeling. Dr. Laniyonu's review contains the details of other studies and the recommended labeling revisions. Additionally, for completeness, Dr. Laniyonu's table of the pharmacology study results is attached to page 24-27 of this memorandum.

Overall the pharmacology-toxicology recommendation is approvable pending adequate data from the following items. I agree with this recommendation; however, in the action letter these items are incorporated into the combined safety deficiency section.

1. The evaluation of microembolic phenomena in animal model with compromised pulmonary function
2. A microcirculation study (e.g., mesenteric artery)
3. Cardiovascular toxicity study

CLINICAL PHARMACOLOGY

The clinical pharmacology and biopharmaceutics aspects of the application were reviewed by Dr. David Lee (team leader) and were found to be acceptable pending labeling revisions and clarifications on the elimination profile of the perfluoropropane (PFP) gas. Specifically, Dr. Lee notes that there are limited amounts of data to document the PFP gas mass balance relationship, the elimination of the PFP and its correlation of these rates with the images, and the lack of assay information. Also, he notes that current technology limits the documentation or complete characterization the metabolic fate of the microbubbles. Therefore, as with other microbubbles underdevelopment, the elimination of the gas is followed as a surrogate. The gas demonstrated a high first pass lung extraction rate in normal subjects and COPD patients. On page 7 of his review, there are subtle differences between normal volunteers and COPD patients; however, the 90% CI is wide and the numbers are not statistically significant. Additionally, although the lipid contents of the microsphere shell are endogenous, the data to identify their metabolic fate were not included in the submission.

Dr. Lee notes that nevertheless, due to the nature of the microbubble drug product", these data are sufficient for an approvable recommendation. I agree with his recommendation. On page 5 of his review, Dr. Lee identified the data deficiencies. These are synthesized to the following:

1. The need for clarification of the assay used in the critical PFP elimination study (DMP 115-905)
2. If these data are not available or acceptable, then a repeat study will be needed.
3. The submission of the literature or other data to validate the metabolism of the lipid microsphere shell.

(Continued on the next page)

CLINICAL – STATISTICAL

DuPont submitted clinical studies of Definity for proposed indications:

“For contrast enhanced ultrasound imaging of cardiac structures (ventricular chambers and endocardial borders).”

These clinical data were reviewed by Drs. Zolman (medical reviewer), Jones (medical team leader), and Sobhan (statistician) with somewhat diverging recommendations. Dr. Zolman recommends notes that efficacy for endocardial border delineation is “at least partially substantiated”. Dr. Sobhan notes that the endocardial border length outcomes data were “marginal”. Dr. Jones’ overall recommendation is that Definity is “approvable for ventricular cavity enhancement and endocardial border delineation/measurement”. Also, he identified outstanding safety deficiencies needing additional study.

I have considered each of their positions and agree

Regarding the cardiac indication there are sufficient data to support ventricular cavity enhancement and endocardial border delineation. Additionally, there are outstanding safety issues; however, the overall application can be considered approvable. the following clinical discussion will focus on the key perspectives that lead to this conclusion.

To support the proposed indications DuPont conducted 17 studies (1 dose ranging, 3 pharmacokinetic-pharmacodynamic studies, 5 safety studies, 5 cardiac critical studies, and

Of these study number DMP 115-004, -005, -006, -007 and -017 were submitted to support the cardiac indications and proposed dosing regimens;

Before DuPont purchased Definity, it was being developed by ImaRx Pharmaceutical Corporation. These studies begin with the prefix MRX and involved approximately 48 patients. The formulation is similar in both the DMP and MRX labeled studies. The clinical database for Definity is derived from the DMP labeled studies.

The following table summarizes the trial identifiers, number of patients who received Definity, the doses of Definity, the number of patients who received placebo, the type of placebo, the design, and purpose or endpoints of the study. The shaded studies are those that are critical to the efficacy assessment. The full demographics of the patients are discussed in the safety section of this memorandum.

Table 5: DuPont Clinical Studies of Definity						
Study ID	N	Doses of DMP 115	N	Placebo	Design *	Type/Endpoints
DMP 115-900	20	5, 10, 20, 50, 100, μ l/kg, placebo,	10	Vehicle	R, SB	Safety
DMP 115-901	16	5, 10, 15, 50, μ l/kg, placebo	6	Vehicle	R, SB	Safety 4 rechallenged
DMP 115-902	42	5, 10, 15 μ l/kg, placebo	14	Vehicle	R, SB	Phase II – cardiac
DMP 115-903	17	2.5, 3.5, 5, 10, 100, 200 μ l/kg	--	--	R, SB, Cross over	Phase II - Multiple dose radiology
DMP 115-905	24	50 μ l/kg – bolus	--	--		PK COPD & volunteers
DMP 115-001	18	10, 30, 50, placebo	6	Vehicle	R, DB,	Phase II - Radiology
DMP 115-002	59	DMP 10 μ l/kg, 10 μ l/kg placebo	18	Saline	R, DB, RBR	IV cavity, EBD
DMP 115-003	100	DMP 10 μ l/kg, 10 μ l/kg placebo	24	Saline	R, DB, RBR	IV cavity, EBD
DMP 115-004	35	DMP 10 μ l/kg	11		Open, RBR	with infusion
DMP 115-005	59	DMP 10 μ l/kg	11		Open, RBR	with infusion
	7	20 – 50 μ l/kg				
	--		--	--		
	42		--	--		
	13	infusion	--	--		
DMP 115-011	59	10 μ l/kg bolus infusion	24		R, cross over, open, RBR	IV cavity, EBD

* R = randomized, SB = single blind, DB = double blind, RBR = randomized blinded read
Shaded = critical to proposed indications
 Derived from Integrated safety summary and medical review

There is a discrepancy in the numbers of subjects identified by DuPont and those identified by the medical reviewer. It is possible that the difference reflects how the patients who received more than one dose of drug, placebo or infusion are allocated. *Clarification of the patient allocation will be requested in the action letter.*

A. Cardiac Indication

The sponsor performed 4 studies that were identified as critical (DMP 115-004, -005, -006, -007) and one study (DMP 115-017) was submitted as supportive of an additional dose regimen. The design of DMP 115-004 and -005 is identical, and the design of DMP 115-006 and -007 is identical. Also, all 5 cardiac studies (DMP 115-004, -005, -006, -007 and -017) had similar enrollment criteria, image handling, and blinded read protocols. The fundamental differences between the protocols are in their endpoints and dosing regimens (e.g., dose, repeat of same dose, cross over to a different dose or regimen). In all studies the eligible patients had suboptimal baseline (non-contrast) echocardiograms. Suboptimal was defined as at least 2 of 6 ventricular border segments that were not evaluative in either the apical 4 or 2 chamber views. Echocardiogram images were read blindly by at least two independent readers for each study. The image analysis was based on the endpoint, the images were read in a paired and unpaired manner and were scored with measures that correlated with the specific study endpoints. These are synthesized in table 6 below. The details of the critical studies are outlined in the reviews of Drs. Jones, Zolman and Sobhan and can be read for more information. This memo will summarize points that are critical to the overall NDA assessment.

DMP 115 Study #	Primary endpoint	Secondary Endpoint
004, 005	Improves Left Ventricular Cavity Enhancement (LVCE) (5 point scale)	Improves in endocardial border delineation (EBD) ¹ Diagnostic Confidence, ability to detect wall motion abnormalities,
006, 007		Endocardial border delineation (EBD) ¹ Wall motion Number of segments with correct wall motion evaluation % of patients with unevaluable segments that became evaluable
017	Left Ventricular Cavity Enhancement (LVCE) (5 point scale)	Segmental Endocardial Border Delineation (EBD) Duration of end systole and end diastole imaging Optimal cavity enhancement Duration of attenuation
<p>1) The terminology of these endpoints is subtly different in each study, endocardial border length and endocardial border delineation. These are considered interchangeable since the border must be delineated in order to measure the length.</p> <p>2) Derived from Dr. Sobhan and Zolman's reviews</p>		

Dosing differences: Study DMP 115-004 and -005 were randomized, cross over studies of a single bolus dose Definity at 5 μ l/kg and 10 μ l/kg versus placebo. Study DMP 115-006 and -007 were open label studies of 2 bolus doses of 10 μ l/kg. Study DMP 115-017 was a multicenter study of 10 μ l/kg versus a 4ml per minute infusion of 1.3 ml of Definity diluted in 50 ml of 0.95 saline.

Based upon the reviews of Drs. Zolman, Jones and Sobhan the following synthesis can be made. The tables used to represent the analysis are from Dr Sobhan's review pages 8 and 14.

1. Left Ventricular Opacification/Enhancement

The critical studies for left ventricular enhancement are DMP 115-004 and -005. The results are summarized in table 7. There was a statistically significant improvement in LVE at end diastole for the 2 and 4 chamber views of the apex and mid chamber.

Table 7*** Intensity (at End-Diastole*) of Left Ventricular Enhancement** – Change from Baseline by Study and Apical Views, Evaluable Patients (10 µL/kg x 2 doses only)					
Study #/Views	N	Apical 4-chamber View		Apical 2-Chamber View	
		Baseline Mean(SD)	Change from Baseline Mean(SD)	Baseline Mean(SD)	Change from Baseline Mean(SD)
Study DMP 115-004:					
Apex					
Placebo	17	15.4(6.6)	3.8(8.5)	18.0(11.7)	2.4(12.4)
Definity™*	33	22.5(18.0)	19.1(17.3)*	22.7(18.0)	13.0(15.8)*
Mid-Chamber					
Placebo	17	13.2(6.2)	2.6(7.0)	15.3(7.3)	1.5(8.5)
Definity™	33	19.1(15.7)	15.8(13.2)*	20.4(17.0)	11.8(13.1)*
Study DMP 115-005:					
Apex					
Placebo	24	26.0(21.5)	2.0(8.3)	27.8(19.8)	-0.7(10.1)
Definity™	49	29.7(20.0)	23.5(21.5)*	27.5(19.2)	22.4(17.5)*
Mid-Chamber					
Placebo	24	20.5(17.3)	0.7(2.7)	21.0(16.5)	1.0(4.0)
Definity™	50	23.8(15.8)	20.8(22.7)*	22.6(15.7)	20.1(18.6)*

* Definity™ = 10 µL/kg x 2 doses
+ Similar results were noted for volumes measured at End-Systole.
++ Intensity measured by videodensitometry.
** Significantly different from placebo and from baseline (p<.05).
*** From Dr. Sobhan's review

2. Endocardial Border Delineation:

The endocardial border delineation assessment is derived from a combination of DMP 115-004, -005, -006 and -007. In studies DMP 115-004 and -005 the EBD was scored as 0=nonevaluable, 1 = evaluable after Definity or after placebo. In study DMP 115-004 there was a statistically significant difference 2 readers found a statistically significant difference in the 4 chamber view and one reader in the 2 chamber view. In DMP 115-005 the differences were not statistically significant. These assessments are considered subjective and minimally supportive.

In DMP 115-006 and -007, the endocardial Border Length (EBL) was measured in centimeters in both apical views at end-diastole and end-systole. As shown in table 8, the mean change in border length from baseline at end-diastole was statistically significant; however, at end-systole the differences were not as apparent.

Table 8 Mean (SD) Endocardial Border Length (EBL) by both Apical 2- and 4-chamber Views at End-Systole and End-Diastole by Study, Evaluable Patients (10 µL/kg x 2 Doses)						
Study/View	Endocardial Border Length –Blinded Read					
	Mean(SD) at End-Diastole			Mean(SD) at End-Systole		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
Study 006 (N=67):						
Apical 2-chamber						
Baseline	8.0(3.4)	4.7(2.8)	6.9(1.6)	7.1(3.3)	4.3(2.6)	6.0(1.5)
Post-Definity™	12.8(5.2)*	5.8(2.6)*	6.2(1.9)	10.6(5.0)*	4.4(2.3)	5.6(1.4)
Apical 4-chamber						
Baseline	8.1(3.3)	4.5(2.6)	7.0(2.3)	7.6(3.2)	4.5(2.7)	6.9(2.6)
Post-Definity™	13.5(5.2)*	6.8(3.3)*	7.2(3.1)	11.5(4.4)*	5.3(3.1)	6.5(2.8)
Study 007 (N=59):						
Apical 2-chamber						
Baseline	4.3(2.6)	7.8(5.3)	7.9(3.8)	4.1(2.4)	6.5(5.1)	7.3(3.3)
Post-Definity™	5.7(4.7)*	8.2(6.5)	7.4(4.1)	5.5(4.4)*	6.9(6.3)	7.2(4.1)
Apical 4-chamber						
Baseline	4.0(2.7)	9.2(5.9)	8.8(4.8)	3.8(2.6)	7.3(5.6)	9.1(5.0)
Post-Definity™	7.1(5.5)*	11.5(7.5)*	7.8(4.2)	5.9(5.3)*	8.7(6.3)*	7.8(4.2)
Definity™ Dose = 10 µL/kg x 2 doses						
* Significant change from baseline (paired t-test, p<0.05)						
** From Dr. Sobhan's review						

3. Wall Motion:

Wall motion was evaluated in study DMP115-006 and -007. A total of 12 segments were assessed with fundamental and harmonic imaging at baseline and after Definity. The results were compared to MRI as a clinical standard of truth¹. The number of segments with an exact match to MRI were evaluated in paired and unpaired blinded reads, and reported as a percentage of the 12 segments. The segments were scored as 0=nonevaluable, 1= normal/hyperkinetic, 2 = hypokinetic, 3 = akinetic, 4= dyskinetic. Also, post hoc analyses was completed by two classifications: Classification I considered 0= nonevaluable, 1= normal, and 2-4 = abnormal. Classification II considered 0 and 1 as normal, 2-4 as abnormal. The classification match was reported as a percentage. Wall motion was similarly reported by region. These measures were analyzed by a paired t-test. (The sponsor states that only the segmental statistical analysis was specified in the protocol).

In study DMP115-006 and -007 for the unpaired and paired blind reads, there is inconsistency in the magnitude of improvement. The sponsor's table attached to page 28 of this memorandum shows that for study DMP 115-006 the unpaired and paired mean difference in segmental wall motion ranges from approximately 22 to 41 % (depending upon the reader). In DMP 115-007 the range is from approximately 1 – 30%. Reader number 5 (third column) was recruited by the sponsor because of the wide difference in the reading results of reader number 3 and 4 in study DMP115-007. Reader number 5 read both studies and had a greater percent improvement in both studies. Also, because reader number 5 read both studies, the reader's results are not independent.

¹ The MRI fast sequences are approved by CDRH and can be used for

and wall motion.

Another concern about the endpoint is that it represents the difference of differences. The actual percent of agreement values could not be located in the submission. If the percent of initial agreement with MRI is high, then small percent of improvement (and small differences of differences) is acceptable. *In order to resolve this, the sponsor will be requested to submit information on the actual percent of agreement with MRI.*

4.

5. Dosing regimen study:

Study 017 is considered as a bridging safety and efficacy study to compare the 10 ul/kg dose of the critical studies to an alternative infusion. As per DuPont and Dr. Zolman's review, the 5 μ /kg dose is associated with attenuation but a shorter duration. The 10 μ /kg dose is associated with long duration but increased attenuation. Data in the animal studies discussed above reveal that the infusion prolongs the imaging duration and decreases the attenuation. The sponsor performed study DMP 115-017 to confirm these findings and to document a similarity in the safety profile of the infusion and the 10 ul/kg bolus.

A total of 64 patients received cross over doses of 10 and 20 μ /kg bolus doses of Definity and 1.3 ml Definity diluted in 50 ml of saline. The bolus could be repeated for image optimization. There was a 24-72 hour minute wash out between the bolus and the infusion. As shown in the sponsor's tables attached to page 29-31, there was an increase in the duration of LV enhancement and a decrease in attenuation with the infusion. Also, the endocardial border delineation and measurements were comparable across all three blinded readers.

Based upon this study, there are data to validate the efficacy of this infusion regimen. The safety of different dosing regimens is discussed in the safety section below.

Overall Cardiac Efficacy Assessment: Based upon the DMP 115- 004, -005, -006, and -007, Definity provides ultrasound contrast enhancement for left ventricular opacification and endocardial border delineation. Based upon DMP 115-017 bridging study, the efficacy of the infusion of 1.3 ml Definity diluted in saline. However, because of the safety concerns discussed below, additional safety data are needed for the infusion. Also, there are insufficient safety data on the 20 μ /kg bolus dose². Until additional data are submitted and found to be acceptable, the recommended doses for labeling should be the 10 μ /kg.

APPEARS THIS WAY
ON ORIGINAL

² The 20 μ /kg dose was not used in the other 4 critical cardiac studies, depending upon the blinded reader,

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pages of trade

secret and/or

confidential

commercial

information

P. 15-16

C. SAFETY

The NDA safety database is derived from a total of 930 subjects (60 normal volunteers and 870 patients) who received either Definity or a placebo during the clinical trials. The distribution of normal volunteers and patients to treatment with a placebo or at least one dose of a DMP-115 concentration is shown in the next table. The allocation of patients referenced in this memorandum are derived from the sponsor's Integrated Safety Summary (ISS); however, there are inconsistencies in the ISS and in the medial review. In several sections, despite the submission narrative to explain the allocation, the numbers are difficult to trace and add. The difficulty may be due to the number of patients that received more than one dose and how they are allocated in the sponsor's tables. *Clarifications will be requested in the action letter.*

	Placebo		Definity	
	Normal Volunteers	Patients	Normal volunteers	Patients
N	16	62	44	809 ^(b)
Age	27.8 (19-42)	56.4 (20-82)	31.8 (19-64)	55.4 (18-87)
Gender	16M/0F	38M/24F	38M/6F	493M/316 F
Race				
White	16	53	39	636
Black		3		112
Hispanic		3	3	42
Other		3	2	19

(a) Derived from the ISE pages 53 – 59; b) Includes the patients who also received placebo

Apparently 843 patients³ received one or more doses of Definity. Of these, 755 (78.7%) received more than one bolus dose and 188 (21.3%) received as infusion dose. The age, gender and racial characteristics were comparable in all dosing groups. The overall exposure to different doses is listed in the sponsor's table attached to page 32.

Of the approximate 881 patients (in the sponsors table page 33) who were exposed to any concentration of DMP-115, 222 (25.2%) had at least one adverse event. Of these there were 5 deaths, 11 serious events and 10 discontinuations.

Deaths: Five deaths were reported. All of these occurred > 15 days after dosing and are not linked to events that began during or in the immediate post dosing period. The patients had an underlying diagnosis of transplant, arrhythmia (7-13 days after Definity), congestive heart failure (CHF), recent myocardial infarction (MI), cancer with surgery 2 days after Definity and pulmonary embolus 5 days after Definity, or coronary artery bypass graft with death 15 days later from multisystem failure and sepsis.

Serious: ~~Serious~~ events were reported in 11 patients. These included exacerbation of CHF, MI 8 days before with percutaneous transluminal coronary angioplasty 1 day after, 3 days after had chest pain and r/o MI; fever, abdominal pain, mental status change, shortness of breath, wound dehiscence, or surgery for underlying disorder. One event of fever was reported at 24 hours. All other events occurred 24 hours to 18 days after Definity.

Discontinuations: There were 10 patients who discontinued because of adverse events. These events began 8seconds to 15 minutes after injection and included chest pain, back pain, headache, and dizziness.

³ The ISE page 53 narrative says 852, but the numbers add to 843.

Of these 3/4 had chest pain that resolved over 1-3 minutes. Also, one patient with decreased pO₂ discussed above, discontinued because of dyspnea and chest pain. This patient was treated with oxygen and resolved over 1.3 hours.

According to the ISE, the most frequently reported adverse experiences headache (3.6%), flushing (2.0%), back/renal pain (1.7%), nausea (1.6%), chest pain (1.4%), injection-site findings (1.2%), and dizziness (1.1%). The medical officer review identified the following laboratory abnormalities: tachycardia and/or bradycardia (30%), anemia (22%), and hypocapnia (3%). Dr. Jones reviewed these abnormalities also. Most changes are considered to be within the range of normal variation. Additionally, the sponsor and Dr. Zolman identified a number of patients that had > 40% increases and decreases in systemic blood pressure. Tables of these patients are attached to the appendix of his review. Dr. Jones considered these patients and determined that the majority of the changes are difficult to interpret and were not associated with clinical symptoms. The sponsor submitted tables that present the change from baseline in clinical meaningful percentages. *To complete analysis, subgroups of patients with various baseline values should be supplied. Also, the results should be analyzed by the dose and infusion regimens. A correlation with heart rate is needed also.*

Placebo: Two different placebos were used. One was normal saline the other was the Definity vehicle (glycerol, propylene glycol and saline). The results were pooled. Data by type of placebo *should be requested*

D. Subgroup assessments:

Adverse Events by dose or dosing regimen: During the development of Definity patients were exposed to a range of doses from 5 to 100 μ l/kg as a bolus and Definity 1.3- 2.6 ml diluted in saline for infusion. Pages 34-35 presents the sponsor's table of all adverse events in all doses of DMP-115, and in combined groups of doses (e.g., < 10, 10-20 and > 20 μ l/kg). Page 36 presents the combined bolus doses and combined infusion doses. Overall, the percentages seem to be similar, however, the events in individual dose groups were not submitted. In order to complete the analysis, this *should be requested*.

Adverse events were reported by indication: the highest percentages of events in these groups are Cardiology: back/renal pain 1.7%, chest pain 1.9%, dizziness 2.2, headache 6.7%, and nausea 2.8% Radiology : abdominal pain 4.3, back/renal pain 4.8%, chest pain 3.3%, and headache 4.8%. Whether these differences are related to underlying disorders or to the higher doses in the radiology studies is not clear.

Adverse events in patients with congestive heart failure or chronic obstructive pulmonary disease: were reported by the subgroup of patients with congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD). (See the sponsor's attached table on page 37-38) Although the sample sizes are small, generally the percent of reported events is similar. However, because of the microbubble issues discussed in the next section (E), there are additional safety concerns in this population.

E. Microbubble Class Assessment

As noted in the chemistry and pharmacology-toxicology sections, there are several focus areas for the safety evaluation of microbubbles. These include the ischemic effects on the pulmonary vasculature or the myocardium. Although the majority (>95%) of Definity microbubbles are less than 10 μ m, the microbubble size/particle maximum of 47 μ m is of concern. Thus far the total number of particles over 10 μ m has not been characterized. The clinical safety reviews completed by Drs. Jones and Zolman focused on adverse events in the pulmonary and cardiovascular systems. During the review, the reviewers requested additional clarifications are the safety database. These were submitted on May 25, 1999. Both

Dr. Jones and Zolman reviewed these data.

1. Pulmonary Adverse Events

Pulse oxymetry data were collected in patients enrolled in studies DMP-115-006, -007, -017, and -902. These studies excluded patients with NY Heart association stage IV disease. As noted in Dr. Jones' review page 6, of the 492 patients, 4 (1%) had approximately 5% decreased in pO₂ within 3 minutes of injection of Definity. Specifically two patients had decreases after the first and second doses of Definity. One patient had a decrease from 95 to 90% after 5ul/kg and to 87% after the 10ul/kg dose. Another patient had a decrease from 98% to 92 % after 5 ul/kg and to 89% after the 10 ul/kg dose. Both patients were either normalizing or normalized by 60 minutes. In study 902, one patient decreased from 95 to 91% with recovery over 45 minutes. Another decreased from 98 to 93% with recovery over 69 minutes.

Another study, 905, compared the safety of 12 normal volunteers and 12 COPD patients. Of the 12 COPD patients, 2 had decreases in pO₂ at 5 minutes or 20 minutes. One patient was symptomatic with dyspnea, and tachycardia. The DuPont phase 3 trials enrollment criteria generally excluded patients with NYHA class IV or severe COPD.

As noted in the overall adverse event table, dyspnea, cough, and other respiratory symptoms occurred in the all patients at <1%.

The interpretation of these events can be illusive. The patients with acute decreases in pO₂, the two with chest pain and dyspnea are suggestive of an acute event such as a micropulmonary embolus. The events in all patients might be from micropulmonary emboli or from other events such as hypersensitivity or underlying congestion and the need to remain in a supine position. Nevertheless, given the particle size concerns and the acute dose, time and rechallenge events, additional data are needed. (See NDA Assessment discussion on the next page)

2. Cardiac Events:

Electrocardiographs (ECG) holter monitoring was completed in normal volunteers in phase 1 dose finding safety studies. Abnormalities were not reported. Holter monitoring was not obtained in patients. Patients monitored with 12 lead ECG data that were collected at different time points at baseline and after 30 minutes (generally). Dr. Jones requested the analysis of QTc intervals in the pivotal trial patients. In these 492 patients, 3/42 (7%) of placebo treated patients and 42/492 (8%) Definity treated patients had QTC interval changes. Dr. Jones notes that the patients were asymptomatic and that the clinical significance of the changes or drug related changes are not known. Also, 15 of these patients received the infusion in study 017. Additional information on any associated rhythm or conduction abnormalities (e.g., BBB, pace maker) was not submitted. *Additional information should be requested.*

Additionally, Dr. Jones requested information on the ECGs of the patients who had acute decreases in pO₂. Definitive correlation's were not noted.

3. Laboratory:

Dr. Zolman's review and the sponsor's ISE note the occurrence of the following laboratory abnormalities: in liver enzymes, calcium, phosphorous and other chemistries. Dr. Jones reviewed the information and concludes that it is difficult to determine whether these isolated changes are clinically meaningful. For the liver enzyme changes the sponsor will be asked to *submit an analysis for the following changes over baseline: 1, 2, 4, and 8 fold increases. This should be presented for all patients and for the degree of baseline abnormality.*

SAFETY UPDATE: A safety update was reviewed by Dr. Jones. The data are similar to that provided in the original submission and are included in labeling.

Division of Scientific Investigations: The inspections did not identify any violative actions that would disqualify the data.

Pediatric Rule Requirements: Pediatric use was not studied during the development of this NDA. Also, the results of studies in immature animals have not been provided. Cardiac ultrasound is used frequently in pediatric populations and the risk of microbubbles in pediatric patients with immature pulmonary vasculature or with congenital cardiac defects associated with right to left should could be associated with undefined risks. In the resubmission the sponsor should identify the pediatric development plan. This should include, among other things, the develop of dosing regimens in high risk pediatric patients.

NDA ASSESSMENT

Definity Kit for the Preparation of Perflutren Lipid Microspheres Injectable Suspension has been sufficiently characterized to support an approvable action for the use of Definity in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders. The use has been demonstrated in adults at doses of 10 μ l/kg and this dose may be repeated once for image optimization. However, there are outstanding safety issues that include the lack of sufficient information to support the infusion regimen, the lack of sufficient manufacturing control to limit the size of microbubbles that might be associated with micropulmonary emboli, and the lack of sufficient data to evaluate the possible risk of QTc interval prolongation. These can be addressed with the exploration of different chemistry procedures plus supportive safety pharmacology studies. Depending upon the results, clinical bridging studies might be needed. Additionally, supportive data are needed to clarify portions of the microbiology and pharmacokinetics sections.

ACTION: Approvable

Letter:

The action letter should identify the following deficiencies or issues:

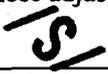
1. []
2. **Safety Deficiencies**
 - a. ~~Insufficient manufacturing control~~ to ensure the safety of the upper limit of the particle size
The discussion should include particle size, pharmacology and clinical adverse events
 - b. ~~Insufficient data~~ to support the use of the infusion
The results from the ongoing study are needed
And Peramifications on the efficacy analysis of study 017
 - c. Insufficient information to analyze dosing and placebo subgroups
 - d. Insufficient information to analyze the liver enzyme elevations
 - e. Insufficient information to analyze the hypertensive and hypotensive measurement fluctuations

3. Insufficient data to assess the mass balance of the PFP gas elimination

4 List all chemistry deficiencies

5 Pediatric rule:

Advise of the requirements to develop safety and efficacy data for pediatrics. Since neonates and infants have immature lungs, they may be particularly susceptible to micropulmonary emboli. Also, dose adjustments in small children are needed.


Patricia Y. Love, M.D.

**- DMP115 4 days vs. 5 min. post vialmixing
Left Ventricular Opacification (1.8MHz)**

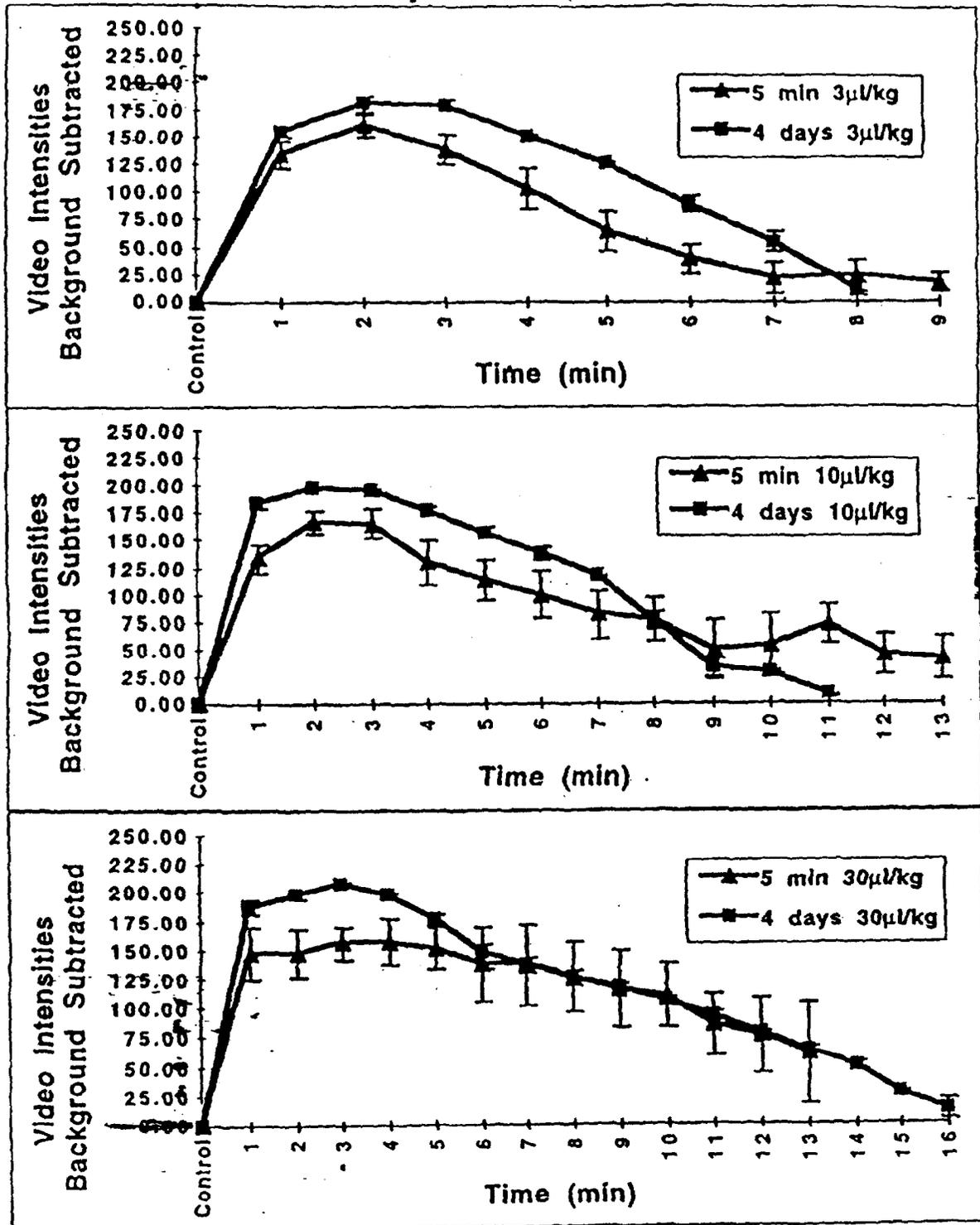


Figure 5. Depicted above are typical background subtracted left ventricular time/intensity curves for DMP115 4 days and 5 minutes post preparation. The top graph represents a dose of 3 µl/kg while the middle 10 µl/kg and the bottom graph 30 µl/kg IV in the canine 2 minute infusion protocol. Each line is the mean ± SEM; N=4 except 30µl/kg 5 minutes where N=3.

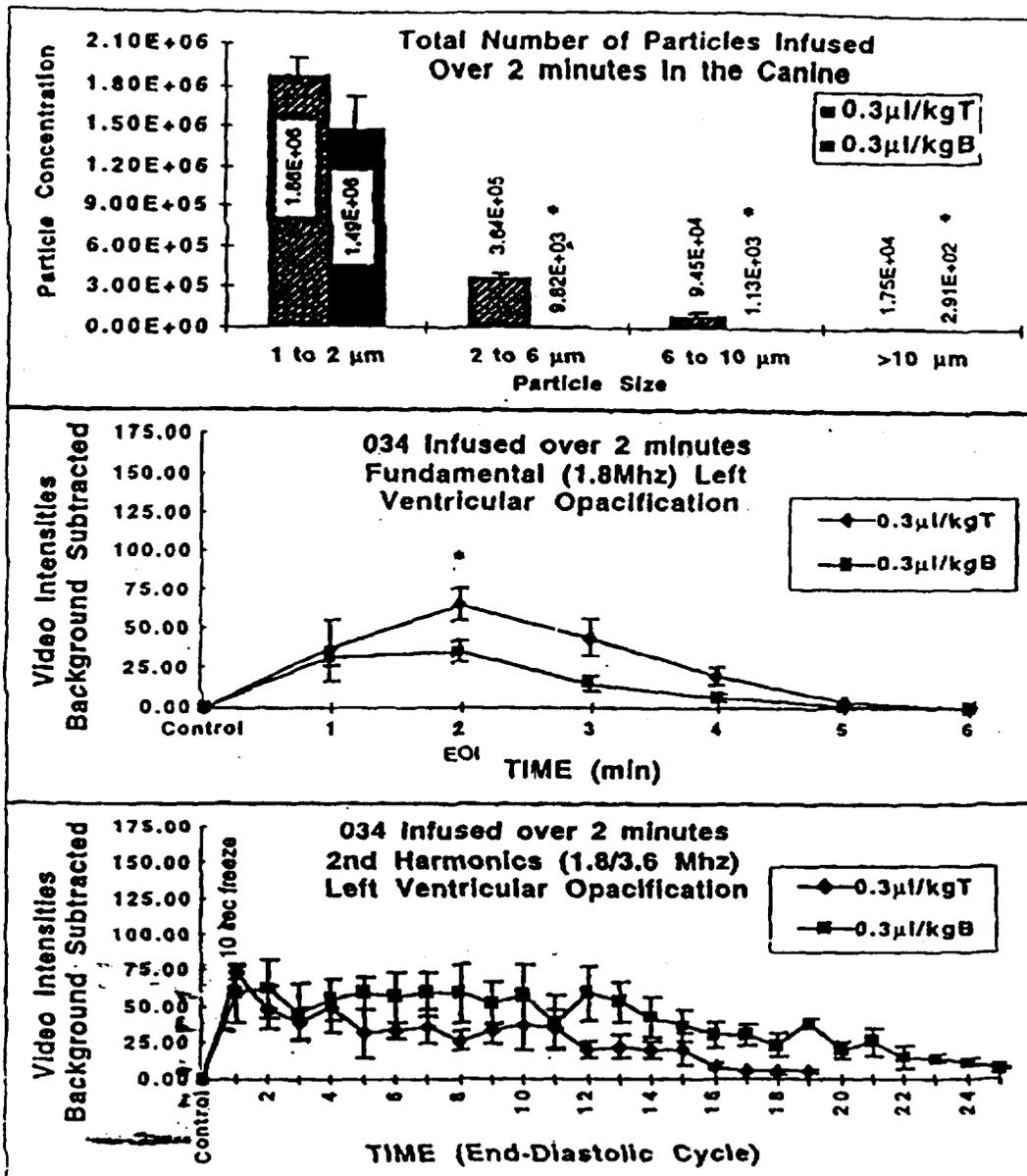


Figure 5. Depicted is the particle size analysis for a dose of $0.3\mu\text{l}/\text{kg}$ and corresponding background subtracted left ventricular video intensities for fundamental and 2nd harmonics. Shown in the top graph is the distribution and number of particles infused in the canine over 2 minutes. The middle graph depicts the left ventricular video intensities for fundamental (1.8 MHz) imaging while the bottom graph shows left ventricular video intensities for continuous 2nd harmonics (1.8/3.6MHz) corresponding to the dose. Each histogram or line is the mean \pm sem for 4 canines. * Indicates significant difference from the top fraction using Student's unpaired t-test ($P \leq 0.05$). T = Top Fraction, B = Bottom Fraction and EOI = End Of Infusion

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Friday, July 27, 2001

BETWEEN:

Name: Mark Taisey and James Adie
Phone: (978) 671-8069
Representing: DuPont Pharmaceutical Company

AND Sally Loewke, M.D. and Thuy Nguyen, M.P.H.

AGENDA: To discuss the Sponsor's faxed letter of concurrence of July 27, 2001, to the draft labeling of July 26, 2001.

The Division stated that the word " " in the Dosage and Administration section of the labeling is being reconsidered. However, if it were to be removed, a new statement will need to be added to the Clinical Trials section of the labeling such as

The Sponsor was reminded that these changes are tentative pending the review with the Office.

ACTION ITEMS

1. The Division will fax to the Sponsor by 5:30 p.m., July 27, 2001, the edited labeling.
2. The Sponsor will submit to the Division a letter of concurrence to the labeling by 10:00 a.m., Monday, July 30, 2001.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Thursday, July 26, 2001

BETWEEN:

Name: Mark Taisey and James Adie

Phone: (978) 671-8069

Representing: DuPont Pharmaceutical Company

AND Sally Loewke, M.D. and Thuy Nguyen, M.P.H.

AGENDA: To discuss the Sponsor's proposed labeling edits of July 19, 2001.

LABELING DISCUSSION

- In reference to the Sponsor's proposed edit to unbold the Cardiac Shunts section of the labeling under Warnings, the Division stated that section will remain bolded due to the positive animal study findings.
- The Sponsor inquired what the marketing impact would be if the section was bolded. The Division will look into the Sponsor's inquiry and get back to the Sponsor with an answer.
- In reference to the Sponsor's proposal to change the time of the second bolus injection from "30" to ' minutes after the first injection, the Division stated that the 30 minutes interval was based on the submitted pivotal trial data. Currently, there is not enough safety data to support the administration of a second bolus injection after minutes following the first injection.
- The Sponsor stated that it would be difficult for a radiologist to hold a patient for 30 minutes in order to give a second injection. The Division understands the Sponsor's position, however, the Division's basis for maintaining the 30 minute interval is primarily one of safety.

- The Sponsor asked that if future Phase 4 preclinical studies show no presence of microbubbles after minutes post injection then would the Division consider changing the "30 minutes" statement in the labeling. This may be a possibility that could be discussed at a later time after the completion and review of the studies.
- In reference to the Sponsor's proposal to remove the word " " from the Dosage and Administration section, the Division stated that we are recommending that the word " " remain in the labeling since there are safety concerns as this is the first time a device is altering a drug. Literature suggests that lower mechanical indices and maybe lower doses are needed with harmonic imaging. The Sponsor inquired if the submitted harmonic data were useful, to which the Division responded that since dosing and device settings for harmonic imaging was not formally studied, the value of the submitted data is limited .
- The Sponsor inquired if the statement in reference to " " imaging will be applied across the drug class. The Division stated that the concern is safety related therefore would apply to the drug class.
- The Sponsor inquired if there is any data that they can submit to support their proposal to remove the word " ". Again, the Division stated that the Sponsor did not fully study harmonic imaging. At this time there are no data to support an appropriate harmonic dose.
- The Division asked if the Sponsor has any microsphere stability data for different modes of ultrasound imaging other than " " to which the Sponsor responded that they do not know.
- The Sponsor stated that technology changes rapidly so it would be hard to repeat Phase 3 studies for every imaging mode, to which the Division suggested a stability bridging study. If future studies demonstrate microsphere stability across a range of device settings then the Division may consider removing the word " " from the labeling.
- The Division informed the Sponsor of minor edits to the Pregnancy Category B section of the labeling and that the word " " will be added to Table 3 of the labeling. The Sponsor agreed to the new edits.

Phase 4 Commitment(s)

- The Division requested an additional Phase 4 commitment:

To perform a one-year adverse event surveillance study on patients receiving activated DEFINITY™ post launch of the product. The protocol will be submitted within 2 months of product launch and implemented within 4 months of design agreement. A final report will be submitted within 6 months of completion.

- The Sponsor stated that only serious adverse events (A.E.) are reported to the Sponsor. The Division would like to have all A.E.s reported for one-year post launch of the product.
- The Sponsor asked if the Division could suggest a method to have all A.E.s reported. The Division is not sure at this time how the reporting could be done, perhaps using callback cards. The Division is asking for a collection of all A.E.s within the first year post product launch not necessarily a new controlled-clinical trial. The Division stated that the Sponsor can submit a protocol and a discussion can pursue at a future time.

ACTION ITEMS

1. The Division will fax to the Sponsor by C.O.B., July 26, 2001, the edited labeling.
2. The Sponsor will submit to the Division a letter of concurrence to the labeling by 11:00 a.m., July 27, 2001.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

MEMORANDUM OF TELECON

DATE: July 23, 2001

APPLICATION NUMBER: NDA 21-064 Definity™

BETWEEN:

Name: Mr. Jim Adie, Mr. Mark Taisey, and Martin Rosenberg, M.D.
Phone: (978) 671-8069
Representing: DuPont Pharmaceuticals Company

AND

Name: Sally Loewke, M.D., and Tia M. Harper-Velazquez, Pharm.D.
Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

SUBJECT: Clarification of issues concerning the adverse event profile and myocardial perfusion studies.

DISCUSSION:

- The division asked the sponsor if they could provide the adverse event profile by bolus for 15 minute versus 30 minute intervals between dosing. The sponsor stated that this information is currently not in the NDA, however it can be provided. The division stated that bolus needs to be broken down by interval of injection. The sponsor can compare 15 minute to 30 minute intervals, and then make a comparison to infusion.
- The division asked if the sponsor was in the process of doing myocardial perfusion studies, and if so, where they are in development. The sponsor responded that they have two myocardial perfusion studies underway, and they regard these studies as Phase 2b confirmatory studies. These two studies are approximately 30% complete and incorporate the use of both radionuclide perfusion imaging and angiography as comparators. Continuous EKG is being performed for 20 minutes during dosing, then a 12 lead is done as soon as imaging is complete.
- The sponsor stated that it is their intent to study myocardial perfusion in Phase 3.

Minutes Prepared By:

/S/

Tia M. Harper-Velazquez, Pharm.D.
Regulatory Health Project Manager

7/30/01

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Tuesday, July 17, 2001

BETWEEN:

Name: Mark Taisey and James Adie

Phone: (978) 671-8069

Representing: DuPont Pharmaceutical Company

AND Sally Loewke, M.D. and Thuy Nguyen, M.P.H.

AGENDA: To discuss the current status of the NDA review.

- The Division informed the Sponsor that the Division has tentatively recommended an approval for NDA 21-064: DEFINITY™, for left ventricular opacification (LVO) and endocardial border delineation (LVEBD) indications. The NDA is now currently under review with the Office.

- The Division will fax to the Sponsor by C.O.B., today, July 17, 2001, the draft labeling for review. The Sponsor is reminded that the language is subject to change as the NDA is currently under review with the Office. The Sponsor was asked to provide demographic data for the Clinical Trials and Adverse Events sections of the labeling.
- The Sponsor agreed to provide the Division with a letter of concurrence to the labeling by July 23, 2001.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Thursday, July 12, 2001, AT 11:00 a.m.

BETWEEN:

Name: James Adie
Phone: (978) 671-8069
Representing: DuPont Pharmaceutical Company

AND Eric Jones, M.D., Thuy Nguyen, M.P.H.

AGENDA: To discuss the mechanical index data that were submitted on July 9 and 11, 2001.

In reference to the mechanical index (M.I.) data submitted on July 9 and 11, 2001, the Division requested that the Sponsor provide a breakdown of the number of patients falling into an incremental M.I. range of 0.2 (e.g. 0.3 to 0.5, 0.6 to 0.8, 0.9 to 1.1, etc.).

The Sponsor agreed to provide the Division with the information by July 13, 2001.

**APPEARS THIS WAY
ON ORIGINAL**

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Thursday, July 12, 2001 AT 9:00 A.M.

BETWEEN:

Name: Mark Taisey and James Adie

Phone: (978) 671-8069

Representing: DuPont Pharmaceutical Company

AND Sally Loewke, M.D. and Thuy Nguyen, M.P.H.

AGENDA: To discuss Phase 4 commitments.

- The Division reminded the Sponsor of the Phase 4 commitments stated in the Division's letter of January 22, 2001. The protocols for the preclinical studies and safety-efficacy profiles (in adults) should be submitted within 6 months of the action letter and implemented within 6 months of design agreement.
- The Sponsor needs to submit a Proposed Pediatric Study Request (PPSR) within 120 days of the action letter. The Sponsor is reminded that their plan under the pediatric rule may not fulfill the requirements for the pediatric exclusivity and vice versa.

ACTION ITEMS

1. The Division will fax to the Sponsor by C.O.B., July 12, 2001, a list of Phase 4 commitments.
2. The Sponsor will forward to the Division by 12:00 p.m., July 12, 2001, a letter of concurrence to the Phase 4 commitments.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Wednesday, July 11, 2001, AT 1:00 p.m.

BETWEEN:

Name: Mark Taisey, B.S., Martin Rosenberg, M.D., and James Adie.
Phone: (978) 671-8069
Representing: DuPont Pharmaceutical Company

AND Sally Loewke, M.D., Eric Jones, M.D., Thuy Nguyen, M.P.H.

AGENDA: To discuss the mechanical index data that were submitted on July 9, 2001.

The Sponsor informed the Division that some harmonic mechanical indices (M.I.) were recorded in studies 006 and 007, in 50-60 patients (in second cardiac imaging not the first imaging). The Division asked if fundamental M.I. were recorded after the first dose up to the range of 1.6, to which the Sponsor replied, yes.

The Division inquired what was the fundamental median to which the Sponsor answered 0.7 (overall median) and the range was

The Sponsor will call the Division by, 4:00 p.m, July 11, 2001, with the fundamental mean.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Wednesday, July 11, 2001, AT 9:00 a.m.

BETWEEN:

Name: Mark Taisey, B.S., and James Adie

Phone: (978) 671-8069

Representing: DuPont Pharmaceutical Company

AND Sally Loewke, M.D., Eric Jones, M.D., Thuy Nguyen, M.P.H.

AGENDA: To discuss the mechanical index data that were submitted on July 9, 2001.

The Division requested that the Sponsor provide a mean for the mechanical index used in the clinical trials that were submitted in NDA 21-064. The mean value will supplement the range and median data that was submitted on July 9, 2001.

The Sponsor agreed to provide the Division with the data by July 12, 2001.

**APPEARS THIS WAY
ON ORIGINAL**

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

RECORD OF TELEPHONE CONVERSATION/MEETING

Date: 7/9/01

I called Jim Adie of DuPont to explain to him that the name "Perflutren Lipid Microsphere" will be conditional pending its acceptance by the United States Pharmacopeia (USP) and will need to be revised if and when USP establishes a different name for Definity drug product. DuPont understood the issue, as this is a qualified USAN name, and will provide acknowledgement of conditional nature of the established name with a commitment to revise the name to be consistent with USP, if and when the USP establishes a different name for the Definity drug product. The acknowledgement and commitment will be send within 2 days.

DuPont also committed to submit one market package of the finished drug product post-approval, when it is available.

NDA# 21-064

Telecon/Meeting initiated by:

 Applicant/Sponsor
 FDA

By:

Ravindra Kasliwal

Product Name:

DEFINITY™

Firm Name:

DuPont

Name and Title of Person with whom conversation was held:

James M. Adie
Sr. Regulatory
Affairs Associate

Phone:

(978) 671-8069

----- /S/ 7/9/01 -----
 Name: Ravindra K. Kasliwal
 Review Chemist

HFD-160

cc : Orig. NDA 21-064
 HFD-160/Division File
 R/D Init. by: Leutzinger

/S/

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: 7/9/01
<p>I called Jim Adie of DuPont to request the updated methods validation package. The updated methods validation package is to address the following:</p> <p>The validation packages submitted on May 2, 2001 contain the _____ method as well as the _____ validation data. The updated _____ method should contain the three-point calibration line and validation data submitted on 31-May-2001.</p> <p>The method for the assay for _____ that was updated to include the resolution criteria in the system suitability testing (provided on 31-May-2001) should be included in the validation package.</p> <p>The validation package does not contain the COA for the lots of lipids, lipid blend and the drug product identified in the submission. DuPont indicated that the available analytical data are old and that the retest data will be available in 2-3 weeks. DuPont asked if the COAs can be provided at the time the samples are submitted. Meanwhile, they will provide a commitment to give us the COA at the time the samples are submitted. After having discussed the issue with Dr. Leutzinger, We agreed to this approach, since the data are really needed by the laboratory personnel at the time analyses are performed.</p> <p>DuPont agreed to provide four copies of the updated validation package by Friday 7/9/01.</p> <p style="text-align: right;">151 7/9/01</p> <hr/> <p>Name: Ravindra K. Kasliwal HFD-160 Review Chemist</p>	<p>NDA# 21-064</p> <p>Telecon/Meeting initiated by:</p> <p><input type="radio"/> Applicant/Sponsor <input checked="" type="radio"/> FDA</p> <p>By: Ravindra Kasliwal</p> <p>Product Name: DEFINITY™</p> <p>Firm Name: DuPont</p> <p>Name and Title of Person with whom conversation was held: James M. Adie Sr. Regulatory Affairs Associate</p> <p>Phone: (978) 671-8069</p>

cc : Orig. NDA 21-064
HFD-160/Division File
R/D Init. by: Leutzinger

151

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Thursday, July 5, 2001

BETWEEN:

Name: James Adie

Phone: (978) 671-8069

Representing: DuPont Pharmaceutical Company

AND Thuy Nguyen, M.P.H.

AGENDA: In reference to the statistical responses in the submission of June 29, 2001.

The Division asked the Sponsor to provide the raw data tables used in the generation of Table 1, in the submission of June 29, 2001.

The Sponsor agreed to provide the Division with the data by July 6, 2001.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Tuesday, July 3, 2001

BETWEEN:

Name: Mark Taisey, B.S., Mark Rosenberg, M.D., Chris Assaid, Ph.D.,
Tsushung (Augie) Hua, Ph.D., Paul Widner, and James Adie.

Phone: 1-(800) 869-6684 (temporary)

Representing: DuPont Pharmaceutical Company

AND Eric Jones, M.D., Joseph Zolman, M.D., Thuy Nguyen, M.P.H.

AGENDA: To discuss the mechanical index.

The Division requested that the Sponsor provide a range for the mechanical index used in the clinical trials that were submitted in NDA 21-064.

The Sponsor agreed to provide the Division with the data by early next week, July 9, 2001.

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Thursday, June 28, 2001, AT 4:30 p.m.

BETWEEN:

Name: James Adie
Phone: (978) 671-8069
Representing: DuPont Pharmaceutical Company

AND Mahboob Sobhan, Ph.D., Eric Jones, M.D., Joseph Zolman, M.D.,
Thuy Nguyen, M.P.H.

AGENDA: To discuss the clinical submission of June 27, 2001 – A.E.
Table 4, and the statistical fax of June 28, 2001.

- In reference to the submission of June 27, 2001, A.E. Table 4, the Division stated that the "Total Number of Patients with AE" = 144, may be incorrect because it may not include all patients who experienced A.E.s. The Division asked the Sponsor to confirm.
- In reference to the statistical fax of June 28, 2001, Table 1, the Division asked that the Sponsor provide total number (N) at baseline – a column is missing for Table 1. Need to provide the number of patients who had 2 or more non-evaluable segments at baseline out of 61. Also, for Table 2, the Sponsor needs to provide the total number at baseline. As of right now, Table 3 looks correct.

The Sponsor agreed to provide the Division with the requested information by June 29, 2001.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

APPEARS
ON ORIGINAL

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Thursday, June 28, 2001, AT 11:00 a.m.

BETWEEN:

Name: James Adie
Phone: (978) 671-8069
Representing: DuPont Pharmaceutical Company

AND Eric Jones, M.D., Joseph Zolman, M.D., Thuy Nguyen, M.P.H.

AGENDA: To discuss the revised adverse event Table #4, in the submission of June 27, 2001.

The Division requested that the Sponsor revise Table 4 "Treatment-Related New-Onset Adverse Experiences occurring in $\geq 0.5\%$ of all DEFINITY™ – Treated Patients" to include total number of patients experiencing an Adverse Event and total number of patients experiencing an Adverse Event by body organ system.

The Sponsor agreed to provide the Division with a revised Table 4, by June 29, 2001.

Meeting ~~Minutes~~ Recorded By: Thuy Nguyen, HFD-160

TCON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Tuesday, June 26, 2001

BETWEEN:

Name: James Adie

Phone: (978) 671-8069

Representing: DuPont Pharmaceutical Company

AND Eric Jones, M.D., Joseph Zolman, M.D., Thuy Nguyen, M.P.H.

AGENDA: To discuss the adverse event Table #4 in the current draft DEFINITY™ labeling.

The Division requested that the Sponsor revise Table 4 "Treatment-Related New-Onset Adverse Experiences occurring in $\geq 0.5\%$ of all DEFINITY™ – Treated Patients" to include total number of Adverse Experiences and total number of Adverse Experiences by body organ system.

The Sponsor agreed to provide the Division with a revised Table 4, by June 27, 2001.

Meeting ~~Minutes~~ Recorded By: Thuy Nguyen, HFD-160

TCON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Wednesday, June 13, 2001

BETWEEN:

Name: Mark Taisey, B.S., Martin Rosenberg, M.D., Simon Robinson, Ph.D., Ronald Gerson, Ph.D., James Adie.

Phone: 1-(800) 869-6684 (temporary)

Representing: DuPont Pharmaceutical Company

AND

Sally Loewke, M.D., R.K. Leedham, R.Ph., Thuy Nguyen, M.P.H.
Division of Medical Imaging and Radiopharmaceutical Drug
Products, HFD-160

AGENDA: To discuss the Sponsor's submission of April 3, 2001.

- In reference to the Sponsor's submission of April 3, 2001, the Division stated that the Sponsor's proposed timeline for pediatric studies may be reasonable under the Pediatric Rule, however, it may not be sufficient for a "Written Request" for pediatric exclusivity. The Division cannot comment at this time if it would be sufficient for exclusivity until the Sponsor submit a Proposed Pediatric Study Request (PPSR) for review.
- Since the Division is in the midst of reviewing the Sponsor's NDA, the Division will forward to the Sponsor a letter detailing what is needed for the Pediatric Rule vs. exclusivity as soon as possible.
- If the Sponsor was to submit a PPSR then the deadline of July 22, 2001, (as stated in the Division's letter of January 22, 2001) would not provide the Sponsor with sufficient time to submit a PPSR. The Sponsor may want to refer to the guidance for industry for information on how to submit a PPSR.
- The pharmacology issues in the submission of April 3, 2001, will be discussed at a later time.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Friday, April 27, 2001

BETWEEN:

Name: Robert Morgan and Mary Matthew
Phone: (978) 671-8069
Representing: DuPont Pharmaceutical Company

AND Ravi Kasliwal, Ph.D. and Thuy Nguyen, M.P.H.

AGENDA: To discuss the chemistry submission of April 19, 2001:
Lipid Blend Specifications.

- In the submission of 04/19/01, there were some inconsistencies in the method numbers used for the lipid blend. The Division asked if the same methods will be used as previously submitted and reviewed, to which the Sponsor answered, yes.
- In reference to paginated pages 14 (bottom section) and 15 (top section) – content uniformity, the Division asked whether the intended amount of PFP still is 6.52 mg/mL and the specification limit is NLT 5.5mg/mL. The Sponsor replied, yes.
- In reference to the vial and carton labeling, the Division stated that the Sponsor should correct the vial and carton labelings to state that 6.52 mg/mL is the target for assay. The Sponsor agreed to make the changes.

ACTION ITEM(S)

1. The Sponsor will submit revised vial and carton labelings with the changes discussed.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

MEMORANDUM OF TELECON

APPLICATION: NDA 21-064

DRUG NAME: DEFINITY™

DATE: Thursday, May 24, 2001

BETWEEN:

Name: Mark Taisey, B.S., Martin Rosenberg, M.D., JoAnne Saye, Ph.D.,
D. Scott Edwards, Ph.D., Paul Widner, M.S., Ronald Gerson, Ph.D.,
Simon Robinson, Ph.D., and Jim Adie.
Phone: 1-(800) 869-6684 (temporary)
Representing: DuPont Pharmaceuticals Company

AND Bayo Laniyonu, Ph.D., Nakissa Sadrieh, Ph.D., Joseph Zolman, M.D.,
Thuy Nguyen, M.P.H.
Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

AGENDA: To discuss the pharm/tox submission of May 15, 2001.

Division asked why DEFINITY™ was not compared to control animal group to which the Sponsor responded that they believed that comparison to baseline control is a more appropriate comparison. The Division requested that individual animal data before and after recalculation be submitted for review.

The Division is concerned that the recalculation was done only in moderate pulmonary hypertension animals and that problems may have occurred in other groups. The Sponsor responded that the calibration review showed no problems in other groups. The Division requested QTc data of the other studies.

The Division stated that the standard deviation error bar of the Figure Graph 6A (see submission dated 05/15/01) showed an animal as an outlier. The Division is surprised that the Sponsor's pharm/tox team did not reanalyze the data. The Division is concerned that the Sponsor did not examine the trend of significant differences between the control and treated animals.

The Division would like to see the steps where the error occurred and what steps were taken to correct it. The Sponsor agreed to submit the individual animal data. The Division understands that severe pulmonary hypertension may have an effect on QTc in just one animal and not all.

The Division requested information on how the Sponsor determined that there was an error in the data from the data acquisition software.

The Division requested graphs of the individual animals from the moderate pulmonary hypertension group.

The Division requested tables showing the individual animal data, from both manual measurements and the Excel spreadsheets from the software for both the moderate and severe pulmonary hypertension groups.

ACTION ITEM(S)

1. Sponsor will submit to the Division the requested pharm/tox animal data by Tuesday, May 29, 2001.

Meeting Minutes Recorded By: Thuy Nguyen, HFD-160

TCON

