

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-064**

Approval Letter



JUL 31 2001

NDA 21-064

DuPont Pharmaceuticals Company
Attention: James M. Adie, Regulatory Affairs
331 Treble Cove Road, Bldg. 600-1
Billerica, MA 01862

Dear Mr. Adie:

Please refer to your new drug application (NDA) dated December 8, 1998, received December 9, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DEFINITY™, Vial for (Perflutren Lipid Microsphere) Injectable Suspension.

We acknowledge receipt of your submissions dated January 30; February 28; March 8, 9, and 26; April 3, 4, 11, 16, 17, and 19; May 2, 11, 15, 16, 18, 22, 30, and 31; June 21, 27, 28, and 29; July 5, 6, 9, 10, 11, 12, 13, 19, 23, 27, 30, and 31, 2001. Your submission of January 30, 2001, constituted a complete response to our action letter of August 4, 2000.

This new drug application provides for the use of activated DEFINITY™ (Perflutren Lipid Microsphere) Injectable Suspension in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter with an expiration-dating period of 6 months for DEFINITY™ drug product vial.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-064." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments and the completion dates agreed upon. Specifically, you have committed to conduct the following:

1. To perform non-clinical studies to determine the fate of the activated microspheres, characterizing the length of microsphere persistence and the potential for microsphere gas exchange. Draft protocols will be submitted within 6 months of approval with initiation of the studies within 6 months of agreement on protocol design. Final study reports will be submitted within one year of study initiation.
2. To complete non-clinical studies of the effects of mechanical ventilation on microbubble characteristics and on the toxicity of activated DEFINITY™. The protocols will be submitted within 6 months of this letter and implemented within 6 months of design agreement.
3. Pending the results of the non-clinical evaluation in item 2, to evaluate the efficacy and safety of activated DEFINITY™ in adults undergoing mechanical ventilation. The protocols will be submitted within 6 months of the completion of the studies in item 2, and implemented within 6 months of design agreement.
4. To perform a surveillance study of adverse events in at least one thousand patients receiving marketed DEFINITY™. The goal is to capture post-marketing safety information on DEFINITY™ as it is actually used in clinical practice. 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.

Submit post market study commitment clinical and non-clinical protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of your commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

Validation of regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27), however, as of January 22, 2001, you have been granted a deferral until post approval. Also, we note your letter of April 3, 2001, in which you expressed your intent to pursue pediatric exclusivity under section 505A of the Federal Food,

Drug, and Cosmetic Act. Based on your intent, we recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. Your proposed pediatric study request should incorporate your plan for addressing pediatric requirements under 21 CFR 314.55. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print.

Please send one copy to the Division of Medical Imaging and Radiopharmaceutical Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We also remind you of your post-approval chemistry, manufacturing, and controls (CMC) commitments/agreements.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Thuy M. Nguyen, M.P.H., Regulatory Health Project Manager, at (301) 827-7510.

Sincerely,

/S/ 7/31/01
(See appended electronic signature page)

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-064**

Approvable Letter



NDA 21-064

Food and Drug Administration
Rockville MD 20857

DuPont Pharmaceutical Company
Attention: Robert A. Morgan
Sr. Director, Regulatory Affairs
331 Treble Cove Road, Building 600-1
North Billerica, MA 01862

AUG 4 2000

Dear Mr. Morgan:

Please refer to your new drug application (NDA) dated December 8, 1998, received December 9, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DEFINITY™, Vial for (Perflutren Lipid Microsphere) Injectable Suspension.

We acknowledge receipt of your submissions dated February 7; March 13 and 31; April 21; June 26; July 5, 10, 12, and 20; and August 1, 2000. Your submission of February 7, 2000, constituted a complete response to our October 8, 1999, action letter.

We have completed the review of this application, as amended, and it is approvable for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. Before this application may be approved, however, it will be necessary for you to address the following:

I. CLINICAL, PHARMACOLOGY/TOXICOLOGY, AND STATISTICAL

A. EFFICACY

1. The application continues to lack sufficient data to validate the use of DEFINITY™ in the evaluation of cardiac wall motion.

As noted in the approvable letter of October 8, 1999, the application lacked sufficient data to validate the use of DEFINITY™ to evaluate cardiac wall motion. Specifically, the letter noted a lack of consistency across readers and studies. The differences in matched segments by reader ranged from 23 to 38% in study DMP 115-006 and 1 to 25% in study DMP 115-007. These results were based upon the results of a 5 point scale with 0 = not evaluable, 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. In response to this deficiency, the resubmission contained a reanalysis with a post-hoc collapsed score of all abnormalities (i.e., the combined scores of 2, 3, and 4). If two readers identified any abnormality, it was scored as abnormal. Also, if all three readers disagreed, then a mismatch with MRI was noted.

Based upon this post-hoc reanalysis, in study DMP 115-006 the concordance with MRI increased from a baseline of 48% to 84% after DEFINITY™. In DMP 115-007, the concordance increased from 47% to 59%. Although the re-analysis provided a single score for comparison with MRI, it did not eliminate the inconsistency between the two studies and this post-hoc selection of the collapsed endpoint may have introduced bias in the analysis. In addition, information was not provided to demonstrate the clinical usefulness of the collapsed endpoint.

The anatomic endpoints of left ventricular endocardial border (LVEB) delineation and left ventricular (LV) opacification have been historically accepted as surrogates for clinically meaningful functional endpoints; but this may not be appropriate for DEFINITY™. Although it has been assumed that improved assessments of LVEB delineation and LV opacification have clinical usefulness (e.g. or wall motion), data have not yet been submitted to demonstrate this for your product. In the literature there are limited data from other echopharmaceuticals on this issue. However, it is not clear whether the literature results are drug specific or transferable to the class of echopharmaceuticals. Because of the potential risk associated with pulmonary microemboli from echopharmaceuticals, it is important to ensure that these products provide clinical benefit. Therefore, before DEFINITY™ can be approved, we request additional documentation that improved assessments of LVEB delineation and LV opacification with DEFINITY™ have clinical usefulness. Such information should include data from additional clinical studies in appropriate clinical settings or data from the literature.

2.

B. SAFETY

1. The upper limits of the particle size distribution of the activated microbubbles lack sufficient manufacturing control to ensure safety of the administered product.

Although we acknowledge the CMC validation of the particle size specifications, we remain concerned about the absolute values in excess of 20 μm . The specifications would allow for a total of 2.4×10^7 particles greater than 20 μm . We note the statements in volume 1, pages 19-20 of your submission of February 7, 2000, that describe many of the characteristics of macroaggregated albumin (MAA). MAA's efficacy is derived in part from occlusion of the pulmonary vasculature. The upper limit of the particle size distribution does not exclude the possibility of severe or serious adverse events. Additionally, because of the risk, the package inserts of MAA products contraindicate their use in patients with severe pulmonary hypertension. The Warnings sections state that there are reports of death occurring after the administration to patients with pre-existing severe pulmonary hypertension.

In order to address the agency's safety concerns, two pre-clinical studies (DRR 2000-01 and RDR-98-08) were conducted. In study DRR 2000-01, the highest dose in group 1 treated animals was associated with increases in pulmonary artery pressure and systemic hemodynamic changes that were consistent with acute pulmonary emboli. We acknowledge your conclusions that these events are related to the total amount of perfluoropropane (PFP) gas (193 $\mu\text{L}/\text{mL}$) and not the total concentration of microbubbles (2.4×10^9). This conclusion is based upon the lack of similar findings in group 2 animals dosed with less PFP (150 $\mu\text{L}/\text{mL}$).

and a higher total concentration of microbubbles (3.9×10^9). In study RDR-98-08, approximately ≥ 0.2 mL/kg headspace PFP gas alone was injected and resulted in deaths in Sprague-Dawley rats. In considering these data, we have the following concerns. First, it is difficult to separate the effect of the PFP gas alone from that of the microsphere size and concentration. Since the gas is insoluble, the injected gas is expected to be contained in the microspheres. As such, the microspheres will be larger when a larger amount of PFP is injected. Therefore, the contribution of the PFP gas alone can not be separated from the contribution of the microsphere particle size.

The time interval between activation and injection suggests that the greatest risk of pulmonary toxicity may occur when the product is administered immediately after activation. In order to determine the risk of toxicity to patients with compromised pulmonary vasculature, as requested in the letter of October 8, 1999, a study in a chronically compromised pulmonary circulation disease model is still needed before approval. This should study a range of dose multiples based upon body surface area. Also, a range of times after activation should be studied.

Although we note the completion of the cremasteric muscle study to evaluate microvascular toxicity, the study used an intravenous injection. As such, the larger particles were filtered by the lungs before reaching the cremasteric muscle. Therefore, we request that this study be repeated using an intra-arterial injection.

We thank you for the particle size data comparing DEFINITY™ with another microsphere product. Any relevant issues will be discussed with that NDA holder.

II. CHEMISTRY DEFICIENCIES

- A. The microsphere size specifications are justified on the basis of clinical and toxicological data submitted in the application. However, as noted in section I.B. of this letter, we remain concerned about the safety of microspheres at upper particle sizes. Based on the concentration of the microspheres in the suspension (maximum 1.2×10^{10} microspheres / mL) and the proposed limit where 0.2% of the microspheres can be larger than ~~20 μ m~~ (up to 47 μ m), the suspension may contain up to 2.4×10^7 microspheres in the large size range. This many larger particles, if present, could create a risk for embolism in susceptible patients. Therefore, as stated in the approvable letter of October 08, 1999, we recommend that the larger particles be eliminated from the injectable suspension.

- B. Please note that if the microsphere size specifications change, information will need to be updated in the method validation packages.

We note the submission of August 1, 2000, in which you requested modification of the time interval between dosing. Our final assessment of this submission is deferred and will be considered with your responses to this letter. Additionally, in order to complete our assessment of the requested infusion dosage regimen, please provide a duration of the infusion with associated documentation.

In addition, it will be necessary for you to submit draft labeling identical in content to the enclosed marked up draft labeling, and the proposed vial and carton labels (actual size and color with overlaid text).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Additionally, we note that the resubmission requests a waiver of pediatric studies based upon the limited use of ultrasound in cardiac imaging. Although we agree that the use of ultrasound is decreasing with the advances of other technologies, ultrasound is a more accessible imaging modality. Because of the safety concerns identified in the clinical section of this letter, we remain concerned that the use in pediatric patients (especially those with immature pulmonary vascular beds) may pose additional risks to pediatric patients. Therefore, pediatric studies are needed to evaluate the safety potential and determine the dose adjustments needed in pediatric patients.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Thuy M. Nguyen, M.P.H., Regulatory Health Project Manager, at (301) 827-7510.

Sincerely,

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FOR

8/9/00

Florence Houn, M.D., M.P.H.

Director

Office of Drug Evaluation III

Center for Drug Evaluation and Research

DuPont Pharmaceutical Company
Attention: Mary Matthew, Regulatory Affairs
331 Treble Cove Road
North Billerica, MA 01862

Dear Ms. Matthew:

Please refer to your new drug application (NDA) dated December 8, 1998, received December 9, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DEFINITY™ (Perflutren Lipid Microsphere) Injection.

We acknowledge receipt of your submissions dated December 15 and 21, 1998; and January 5, 11, 13 and 19; February 1 and 11; March 3, 5 (2), 12, 23, 26 and 29; April 7, 14 and 15; May 3, 13, 18, 25 and 28; June 23 and 24; July 12, 19 and 27; and August 3 and 11, 1999.

We have completed the review of this application, as amended, and it is approvable for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in doses of 10 µl/kg. Before this application may be approved, however, it will be necessary for you to address the following:

I. CLINICAL AND STATISTICAL

A. EFFICACY

1. The application lacks sufficient data to validate the use of DEFINITY™ in cardiac wall motion.

Wall motion was evaluated in studies DMP-115-006 and DMP-115-007. One outcome measure was the difference in the percentage of segments matched exactly in grade of dysfunction between MRI and echocardiography before Definity™ with the percentage of segments matched between MRI and echocardiography after Definity™. The results of the blinded reads were not entirely consistent across the two studies or across readers. For the blinded unpaired reads, the differences in percentages of matched segments after Definity™ administration compared to the percentage matched at baseline ranged from 23% to 38% depending on the reader in study DMP-115-006. These percentages ranged from 1% to 25% depending on the reader in study DMP-115-007. Similar results were noted for the paired reads. The standard

deviation for all reads ranged from approximately 16-30. Although some of these differences were statistically significant, in 60% of the segments a match was not achieved. Moreover, reader #5 was selected after the initial analysis was completed, and the reader's interpretations are not independent across the two studies.

2.

B. SAFETY

1. The activated microbubble upper limits of the particle size distribution lack sufficient manufacturing control to ensure safety of the administered product.

The chemistry and animal pharmacology data indicate that the optimal imaging characteristics are dependent predominantly on microbubbles less than 10 μm in diameter. The manufacturing specifications indicate that the largest allowed

particles are 47 μm in diameter. Particles of this size are known to be associated with micropulmonary embolism.

The safety pharmacology section contained several cardiovascular studies that monitored pulmonary and cardiovascular pressures in different species. In all of these studies the human dose multiples were very low. Specifically, the maximum human dose multiples based on body surface area were 0.03 in rats, 0.81 in dogs, 0.5 in pigs, 5.5 in rabbits, and 1.62 in monkeys. Across these species the pulmonary artery pressures were either normal or elevated at these dose multiples. In rats and one dog there were histologic changes consistent with pulmonary congestion. Because of the low dose multiples of these studies and the inconsistency across species, these studies are not conclusive.

The clinical data revealed two patients (DMP-115-006, site 1, #6 and DMP-115-007, site 4, #6) that had a decrease in pO_2 after each of two doses of DEFINITY™. Two patients (DMP-115-902, site c #33 and #36) had decreases in pO_2 that required 45-69 minutes to normalize. A third patient (DMP-115-905, #8) had decreased PO_2 with symptoms of tachycardia and dyspnea.

While these collective sets of data are not conclusive for the occurrence of micropulmonary emboli, they are suggestive. In order to resolve this deficiency the following are recommended:

- a. Adjust the manufacturing controls to ensure that particles are $\leq 10 \mu\text{m}$ in diameter.
Alternatively, the manufacturing process could be adjusted to ensure compliance with USP requirements for particulate matter. Validation of the approach will be needed as stated in the Chemistry Deficiencies.
 - b. Completion of a special pharmacology safety study to evaluate the risk in a chronically compromised pulmonary vasculature disease model. This should include a rigorous assessment at a wide range of human dose multiples adjusted for body surface area.
 - c. Depending upon the manufacturing approach taken and the results of the special safety study, additional clinical bridging studies may be needed.
2. The application lacks sufficient data to characterize the risk of arrhythmias.

An analysis of the electrocardiographic QTc intervals (submitted May 25, 1999) revealed 35-42 of 492 patients with QTc prolongation greater than 0.03 units. Such prolongation might be associated with torsades de pointes. The submitted analysis also did not provide information on the rhythm or other conduction abnormalities that might have occurred in the patients. Also, these abnormalities were identified at 30 minutes after administration of DEFINITY™. ECGs were

not obtained at earlier time points (e.g., immediately after injection or during the infusion) when the risk may be greater.

The animal safety pharmacology studies used to evaluate electrocardiographic and contractility parameters were the same studies discussed in item II.A above. Therefore, the dose multiples are too small to support definitive conclusions. Also, there were two toxicology studies that used higher doses (48 MHD and 162 MHD). In these studies there were findings of ventricular tachycardia, AV block, and bundle branch blocks. However, these studies were not designed to comprehensively evaluate the cardiovascular system. As such, the pre-clinical database does not contain sufficient information upon which to base the risk of acute cardiovascular adverse events. Also, data on the potential for systemic clumping, aggregation or coalescence was not provided.

Therefore, the evaluation of the risk of QTc prolongation, rhythm disturbances or other myocardial conduction abnormalities can not be completed. In order to resolve these deficiencies the following are requested:

- a. The completion of a safety pharmacology cardiovascular study using a wide range of human dose multiples based upon body surface area. This may be accomplished in conjunction with the pulmonary vasculature study requested in the preceding section.
 - b. An *in vivo* evaluation of the potential for clumping, aggregation or coalescence in the systemic circulation (e.g., a microvascular model such as a mesenteric artery, cheek pouch, or retinal vessels).
 - c. The provision of information on the rhythm or other conduction abnormalities that were associated in the patients who had prolongation of the QTc interval greater than 0.03 units.
 - d. Depending upon the outcome of these data, additional clinical bridging studies may be needed.
3. The submission lacks sufficient data to complete the adverse event risk assessment.

Specifically the adverse events associated with the two placebos (the DEFINITY™ vehicle and saline) were pooled. Also, the adverse events associated with different doses were pooled in groups (e.g., < 10 µL/kg, 10-20 µL/kg, and > 20 µL/kg.). This may obscure a trend analysis. Please submit an adverse event table that separates the events of each placebo. Also submit an adverse event table that compares each dose given by bolus and by infusion.

4. The submission lacks sufficient data to characterize the safety profile of the infusion of 1.3 ml DEFINITY™ in 50 ml saline in echocardiography.

Study DMP-115-017 was conducted to compare the safety and efficacy of the bolus dosing regimen used in the pivotal studies (DP-115-004, -005, -006 and -007) with the infusion of 1.3 ml DEFINITY™ in 50 ml saline. A total of 64 patients were studied in a crossover manner. While the data suggest the similarity of the safety profile, given the safety concerns identified in I.B.1 and I.B.2 above, additional data are needed in patients who receive the infusion. It is our understanding that other cardiology studies using the infusion are ongoing. Data from these studies should be submitted. Also, as discussed in the preceding sections, the infusion dose should be included in all repeat pharmacology studies and, if needed, in any bridging clinical studies.

5. The submission does not include data on reproductive toxicology studies performed with the final to-be-marketed formulation. We note that you plan to submit such data to FDA in the first quarter of year 2000.

II. CLINICAL PHARMACOLOGY

- A. The pharmacokinetics data lack sufficient information to validate the results of the octafluoropropane elimination profile.

Specifically, study 905 was performed to measure the elimination of the octafluoropropane gas. The data to validate the assay were not submitted. In order to resolve this deficiency, please provide the assay validation data. Alternatively, if these data are not available or are not sufficient, the mass balance study should be repeated.

- B. The elimination data lack sufficient information on the fate of the microsphere shell.

Although the application states that the lipid components are endogenous substances, data to characterize the elimination were not submitted. In order to resolve this deficiency, please provide an analysis of the pharmacokinetic literature on these components as a liposome. If literature data are not available, then studies are needed to demonstrate whether and how the microsphere shell is metabolized and/or eliminated.

III. CHEMISTRY DEFICIENCIES

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secret and/or

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information

(PPs. 7-25)

- b. To submit all stability study results in the annual report submitted to the Agency.
- c. To withdraw from the market any batches found to fall outside of the approved specifications for the drug product.

G. CONTAINER / CLOSURE

1. The application lacks sufficient container / closure information.

- a. Provide a copy of representative _____ of the stopper formulation for the _____ stoppers.
- b. The _____ stoppers are apparently _____ prior to their use. The information on the compound used for _____ is not provided. Provide the name, product code, manufacturer, and DMF number with appropriate letter of authorization for the compound used for _____ the stoppers.
- c. Because of the nature of the drug product and the nature of the component present in the headspace, we are concerned that the _____ used in the stoppers may be extracted into the drug product matrix. Provide information on the amount of _____ that can be potentially be extracted into the vial and justification for the safety of such amounts.
- d. Provide the composition, color and the dye used in the _____ of the container / closure seal. Also, identify the composition of the interior crimp seal used for DEFINITY™ container / closure.
- e. Provide full description of all outer packaging that will be used with DEFINITY™.
- f. Provide draft labels that would be placed on the vials, and each outer container. The carton label will need to contain:
 - The established name of the drug as well as the dosage form in _____ juxtaposition with the proprietary name.
 - An accurate statement of strength; i.e., the concentration (mass / volume) of octafluoropropane in the headspace of the vial.
 - The name and quantities of all ingredients, as well as the name and quantity of the active ingredients, in terms of microbubble concentration, PFP in the liquid phase and size distribution.
 - The legend "Caution: Federal law prohibits dispensing without

- prescription”, or “Rx only”
 - Statement “For Intravenous Administration”
 - Lot Number and expiry date.
 - Statement “Sterile, non-pyrogenic, contains no bacteriostatic preservative”.
 - Statement for “store between 2° - 8°C (36° - 46°F) in a refrigerator.
 - Statement in bold “ **NOT FOR DIRECT ADMINISTRATION**”
 - Statement concerning the use and expiry of the activated product”.
 - Volume in the container.
 - Statement “FOR SINGLE USE ONLY”.
 - Statement “NOT EQUIVALENT TO OTHER DRUG PRODUCTS CONTAINING PERFLUTREN” should be prominently placed on at least two sides of the carton label as well as the package insert.
2. Please note that once the suitability of the specifications and methods has been determined the updated method validation packages should be submitted.
 3. The application lacks sufficient information concerning the Vialmix™ shaking apparatus.
 - a. Submit diagram(s) showing the relevant construction and appearance of the Vialmix™ apparatus to the NDA.
 - b. In the clear off-white-gray area, adjacent to the green area where operating buttons are located, a label describing the intended use and procedure for the preparation of DEFINITY™, and improper use and function warning, should be affixed. The label should also have phone number that users can use to contact Du Pont for questions concerning the use of Vialmix apparatus. Provide a copy of the label, with contents, that would be placed on the Vialmix™.
 - c. Provide the procedures that would be used by Du Pont to assure that DEFINITY™ is only shipped to users that have the Vialmix™ apparatus. Specify the Vialmix™ calibration procedures and the recommended schedule.
 4. Specify whether training will be provided to the users for the preparation and use of activated product.

In addition, it will be necessary for you to submit draft labeling revised as enclosed marked up draft labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Additionally, because of the safety concerns identified in the clinical section of this letter, the use in pediatric patients (especially those with immature pulmonary vascular beds) may pose additional risks to pediatric patients. Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. Please submit your pediatric drug development plan or request a waiver with supporting information and documents.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment

should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Kaye Cho, Pharm. D., Regulatory Project Manager, at (301) 827-7510.

Sincerely,

/S/

Victor F. C. Raczowski, M.D., M.S.
Office Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 21-064
HFD-160/Div. Files.
HFD-160/Cho
HFD-160/Zolman/Jones/Laniyonu/Sadrieh
HFD-870/Lee
HFD-720/Sobhan
HFD-820/Kasliwal/Leutzinger
HFD-805/Riley/Cooney
HFD-002/ORM
HFD-103/ADRA
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

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