DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-899/SCM-007

Mallinckrodt Inc.
Attention: Edward Porter
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134

Dear Mr. Porter:

Please refer to your supplemental new drug application dated October 31, 2001, received November 2, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Optison (Human Albumin Microspheres) Injectable Suspension Octofluoropropane Formulation.

We acknowledge receipt of your submissions dated July 8, August 27, September 23, October 8, November 24, 1998; June 21, August 2, September 13, October 17, 19 and 27, 2000; and October 31, 2001; February 28, March 1, 6, 7, 13, 14, 15, and April 9, 2002. Also, we reference our teleconferences of September 24 and November 24, 1998, February 27, March 1 and 28, 2002 and meeting August 31, 2000.

This supplemental new drug application provides for 1) the change in the manufacturing process for Optison from the current (b)(4)----------and 2) the change of the site of manufacture of the----------
(b)(4)-----
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We have completed the review of this supplemental 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 stated in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the agreed upon draft labeling (package insert submitted April 9, 2002).

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 heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-899/SCM-007." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated March 1, 2002, to obtain Pharmacology/Toxicology studies using product made with the new (b)(4)---------- manufacturing method. These commitments are listed below.

1. SAFETY PHARMACOLOGY STUDY

A comprehensive safety pharmacology study in a large species (monkeys or dogs) at various dose levels (with high dose multiples). The study must include a complete battery of CVS (including continuous ECG monitoring, with emphasis on QT interval), CNS, renal, and respiratory (pulmonary arterial pressure/resistance etc.) parameters. The ECG must include a range of mechanical index values and systolic triggering. Also, include *in vitro* electrophysiological studies evaluating effects on cardiac action potential or potassium channels. The study must be carried out in unanesthetized animals and statistical analysis must be performed on the whole data generated.

2. EFFECTS ON MICROVASCULATURE

A study to visualize the behavior of the microspheres in the microvasculature. The study must be conducted using an appropriate model, for which the FDA provides concurrence, using intraarterial administration. Vessels with diameter less than 10μm must be examined for the microvasculature study. Microspheres must be visualized using intravital microscopy. Data must be acquired for as long as the microspheres are visualized. Microsphere size and deformability must be documented. The percentage of capillaries obstructed must be reported.

3. ANIMAL MODEL WITH COMPROMISED PULMONARY FUNCTION

A study in an appropriate animal model with pulmonary microvascular compromise. Parameters such as pulmonary artery pressure/resistance, blood gases, respiratory and cardiac functions (such as ECG) must be assessed.

4. ULTRASOUND EFFECTS ON OPTISON AND ENDOTHELIUM

A study characterizing Optison microsphere after exposure to ultrasound. Data to be provided must include

1. Histopathological data after exposure to the range of available mechanical index values. Areas study must include the myocardium, kidneys, carotids and abdominal vessels. Possible consideration should include endothelial injury.

2. Data to document the fragility of the microspheres after exposure to maximally available range of index values.

3. Potential effects on cardiac electrophysiology (e.g. action potential duration)

5. EXCHANGE OF GAS AND DURATION OF THE MICROSPHERES

Provide data to evaluate the possibility of gas exchange, which might affect microsphere size and associated toxicities.

6. PHARMACOKINETCS OF INTACT MICROPSHERES

Describe the addition of Optison to blood or plasma and evaluate results by microscopic examination to gather information on the microsphere population, the rate and time of disappearance, duration of microsphere detection, % aggregation or coalescence rate, etc.

Before implementation, the protocols for these studies should be submitted for review and comment. Draft protocols must be submitted within 9 months of this letter. (This may be staggered across 9 months). The studies must be initiated within 6 months of the protocol agreement. The results must be submitted within 6 months of study completion.

We also remind you of your postmarketing study commitment in your submission dated April 9, 2002, that upon completion of 30 commercial batches of (b)(4)-------Optison, to tabulate and analyze the data and set new specification limits for the mean ----------distribution that are based upon the process capability demonstrated in the larger database. The data for all the parameters should be analyzed and the results submitted to the FDA within 4 months of completing 30 commercial batches and if the data so indicate, the acceptance criteria will be tightened for any or all indicated size distribution parameters.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to these NDAs. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. 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."**

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Patricia A. Stewart, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Patricia Y. Love, M.D., M.B.A.
Director
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Patricia Love

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