447 March Road
Kanata, Ontario
Canada K2K 1X8
Tel: 613 592-2790

MDS Nordion
Science Advancing Health

January 19, 2000

John T. Yankovich
Senior Engineer
Sealed Source Safety Section
Division of Industrial and Medical Nuclear Safety
Office of Nuclear Materials Safety and Safeguard
United States Nuclear Regulatory Commission
Mail Stop: T-8F-5
2 White Flint North
11545 Rockville Pike
Rockville, MD
20555

Dear Mr. Yankovich:

Your letter dated November 23, 1999 with comments pertaining to our registration request for the device, TheraSphere, was received by fax on December 15, 1999 and by mail on December 17, 1999.

The following responses to your comments are presented in the same numerical order as in your November 23, 1999 letter:

Comment:

1. Provide a drawing, showing the major dimensions, for the "12 mm lucite vial shield" and its closure (as described on page 2 and shown in Figure 1 of the application). The drawing should also illustrate the cavity for the glass vial containing the microspheres:

   Response:
   The acrylic shield is illustrated in drawings K120612-003, -004, -005 and -006. (Attachment 1,2,3,4)
   A composite drawing of the lead pot and acrylic shield is provided in Attachment 8.

Comment:

2. Provide a drawing, showing the major dimensions, for the lead shield in which the lucite vial is stored and transported. The drawing should illustrate the cavity for the lucite container. An assembly drawing for Items 1 and 2 is also acceptable if it displays the information, which we request.

Response:
The F-390 lead shield in which the lucite vial is stored and transported is illustrated in drawings F139001-003, -004 and -005. (Attachment 5,6,7)
A composite drawing of the lead pot and acrylic shield is provided in Attachment 8.

3. Regarding labeling, please specify

Comment:

a. the material, thickness and adhesive characteristics of the label which you intend to use on the lead-pot/lucite-shield (page 7 of the application);

Response:
The laser label materials for the lead pot and lucite shield are the same. The label face materials is a 60# matte litho, 3.4 mils thick with a superior smooth surface for laser printing. The adhesive is E117, a water based, acrylic and permanent with high shear strength and good initial tack. The liner is B85, a hygroscopically stable coated paper that has excellent "flatness" properties as required for laser printers.

Comment:

b. the handling and storing instructions as required by 10 CFR 32.74 (a)(2)(viii);

Response:
The statement on the product label "See package insert for directions for use"
will be updated to say "See package insert for directions for use, handling and storage"

The package insert also will be revised to add the following section:

Handling and Storage
Each dose vial of TheraSphere contains 5 to 20 GBqYttrium-90, a high-energy beta emitter. Even with low-density materials such as the product's lucite shield, the attenuation of beta particles gives rise to Bremsstrahlung which requires lead shielding. Users should avoid exposure by leaving the vial in the lucite product container, and by leaving the lucite container in the lead shield as much as possible. The use of additional shielding is recommended. Finger ring dosimeters should be worn in the orientation most likely to record the highest exposure to the fingers

The product should not be removed from its lucite shield. It should be stored in the lead pot and lucite container in which it is packaged. The requirements of the applicable regulatory agency for safe handling and storage of radioactive materials should be consulted and must be adhered

to. A copy of the revised package insert which contains other changes as recommended by the Center for Devices and Radiological Health (including the above Handling and Storage Section) is attached. (Attachment 9)

Comment:

c. how you will designate the activity level as required by 10 CFR 32.74 (a)(3).

Response:

The terminology "Calibration", on the lucite and lead pot label, will be changed to "Date of Assay" to comply with the requirements of 10 CFR 32.74 (a) (3).

The following statement will also appear on the product label:
The U.S. Nuclear Regulatory Commission has approved distribution of TheraSphere to persons licenced to use byproduct material identified in 35.57, 35.400, or 35.500, as appropriate, and to persons who hold an equivalent license issued by an Agreement State.

Comment:

4. Specify if you use serial numbers to identify each TheraSphere dose. If yes, please indicate where the serial number is located and how durable the identification is. If no, describe why individual dose identification is not needed.

Response:

As shown on **Page 7, Labelling** of the original submission the lot number of the product is identified as "lot" on the product label. A copy of this page has been appended. (Attachment 10)

To test the durability of lettering which was applied to the product label, the label was subjected to an alcohol wipe test, a drug wipe test, a wet wipe test and a temperature/humidity test, as described in Attachment 11. The test results showed that the paper stock passed all tests. The printed image, the printing and the paper remained intact.

Comment:

5. Regarding prototype testing, we understand that testing of individual microspheres has not been performed by MDS Nordion, due to the limitations of their microscopic size. Therefore, please provide historical data on the TheraSphere devices (i.e. microspheres in the lucite container) that have been manufactured over the years and used in other countries. Specify how many years they have been in use and what accident conditions they have survived. State that the products are identical in size and construction, and whether or not problems have been encountered in transportation, handling and in clinical practice.

Response:
TheraSphere has been manufactured by MDS Nordion for 9 years and has been distributed within Canada, Taiwan, and South Africa. There are no records on file of problems with transportation, handling and in clinical practice.

The size distribution of the microspheres and their chemical composition has not changed in the past nine years.

Comment:

6. Provide prototype test information on the lucite shield and its closure illustrating transportation accidents and accidental drops likely to be encountered during storage and use. For example, you may show how it retains its content if dropped from a height of 1 m to a typical hospital floor.

Response:
Qualification tests were performed on the F400/F390 type A transport package. These tests included a water spray test, a drop test and a penetration test on the F400/F390 transport package containing TheraSphere, F390 lead pot, and administration kit. These tests are documented in MDS Nordion Report IS/TR 1190 F400/F390. (Attachment 12) The F390 lead pot, lucite shield and contents suffered no visible damage from the water spray or the 9-meter drop test.

Subsequent to the type A testing, the F390 lead pot was subjected to two penetration tests without the F400 packaging. The penetration test was performed by dropping a 1.25 in. diameter bar weighing 6-kg from a height of 1 metre. Two tests were performed on the F390 lead pot with the acrylic shield and glass vial inside. The first test impacted the pot on its side at mid height. This caused a dent approximately 4 mm deep in the lead pot. The second test impacted the pot at the body/cap interface. This caused a partial separation of the lid, but it still remained firmly attached. Also, the acrylic shield cracked near the top, but did not break. The glass vial was not damaged as a result of either test.

Attachment 13 is a Test Report describing drop tests for the F-390 lead pot and TheraSphere acrylic shield. The lead pot and acrylic shield were dropped from one meter in various orientations onto a concrete floor and demonstrated that this type of containment could withstand normal handling accidents which might occur in a hospital environment.

7. Regarding external radiation levels, NRC needs information on the device itself, not on the radiation levels around the patient as addressed in the application. Therefore, please specify;

Comment:

a. External radiation levels around the lucite vial containing the maximum dose of 20 GBq (540 mCi). Provide the data, preferably, at the surface, and at 5, 30 and 100 cm. If there are no meaningful readings at these locations, please state so.

Response:

The external radiation levels for a lucite vial containing 515 mCi of Yttrium-90 are presented in the study report *PD99099003.08, Investigation Study Radiation Profile on a 20 GBq TheraSphere Dose Vial*, (Attachment 14). This study compares the radiation levels when the lucite shield is placed in the F390 lead pot.

Comment:

b. Provide similar external radiation levels, if any, outside the lead pot with the lucite vial inside containing a maximum dose of microspheres.

Response:

The external radiation levels for an F390 lead pot containing a vial of 515 mCi of Yttrium-90 in its lucite shield are presented in the study report *PD99099003.08, Investigation Study Radiation Profile on a 20 GBq TheraSphere Dose Vial*, (Attachment 14). This study also compares the radiation levels when the lucite shield is removed from the lead pot.

Comment:

c. Please specify the instrumentation, which you used to perform the radiation profile measurements by listing the instrument manufacturers, model numbers, calibration dates, sensitivity, etc.

Response:

Two instruments as described in study report PD99099003.08, Investigation Study Radiation Profile on a 20 GBq TheraSphere Dose Vial, (Attachment 14) were used to measure external radiation levels for the lucite shield and the lead pot containing the lucite shield. The study was performed in December 22, 1999.

The Victoreen Model 471 survey meter, MDS Nordion No. 6-144-282 is calibrated monthly on-site in a facility approved by the Atomic Energy Control Board and United States Nuclear Regulatory Commission. The calibration date was November 25, 1999. Information on instrument sensitivity appears in attachment 15.

The Extender 2000W survey meter, serial number #2808 and MDS Nordion No. 6-144-569, is manufactured by Wm. B. Johnson and Assoc., and is calibrated every 6 months. It was calibrated in December, 1999 and is scheduled for recalibration in May, 2000. Information on instrument sensitivity appears in attachment 16.

Comment:

d. Provide the annual occupational dose rate to personnel administering the microspheres. Base your calculation on how many administrations a person would likely complete in a year, how much the activity level in a kit could be on the average, and on how long each procedure would take. In your response, please describe the assumptions on which you base your calculations.

Response:

Two articles are provided for reference purposes:
Houle S., YipTsui-Chun K., Shepherd F.A., Rotstein L.E., Sniderman K.W.,
Theis E, Cawthorn R.H., Richmond-Cox K. Hepatocellular Carcinoma: Pilot Trial of Treatment with Y-90 Microspheres, Radiology, 172:No. 2, 857-860, 1989. (Attachment 17)

Gordon, K., Greenberg, I.D., Huda W. Radiation Protection Aspects of Y-90 Radiotherapy for Malignant Tumors. Abstract Society of Nuclear Meeting, 1991. (Attachment 18)

The article by Gordon et al summarizes dose rate and the time integrated radiation dose measurements taken by ionization chamber and TLD's for several days post treatment and shows that the total two day integrated dose at approximately 2 meters from the patient was less than 10 mrads. Radiation exposure to personnel was studied by Houle et al. They concluded that use of vials sealed in a lucite shield, additional lead shielding to guard against bremsstrahlung radiation and the use of a double layer of surgical gloves and long forceps kept the extremity exposure of personnel to less that 0.2 mSv per administration.

It is assumed that on an annual basis, 48 patients could be treated at any one site and that two physicians would share the responsibility of dose administration. The total annual extremity dose would then be less than 4.8 mSv.

Comment:

8. Procedure No. 990602.SPE refers to Yttrium-89. Specify that it applies to Yttrium-90 used in the manufacture of the microspheres for the TheraSphere device.

Response:

The Yttrium-89 Glass Microspheres which are characterized in Specification No. 990602.SPE are not radioactive. It is these microspheres which will be irradiated to produce Yttrium-90 Glass Microspheres. To release this lot of "cold" microspheres, for use in routine production of Yttrium-90 Glass Microspheres, a

sample of the microsphere will undergo irradiation and must meet the specifications for radionuclidic purity and yttrium-90 release as shown in this specification.

Should further clarification be required, please do not hesitate to contact me.

Yours sincerely,

Ann Warbick Cerone
Manager, Regulatory Affairs
Tel: (613) 592-3400 Ext. 2033
Fax: (613) 591-7481

Attachments:

Attachment 1 - K120612-003 : Shield Assembly
Attachment 2 - K120612-004 : Shield, Base
Attachment 3 - K120612-005 : Shield Cap
Attachment 4 - K120612-006 : Shield, Access Plug
Attachment 5 - F139001-003 : Cap (F-390)
Attachment 6 - F139001-004 : Body (TheraSphere) (F-390)
Attachment 7 - F139001-005 : Lead Pot Assembly (TheraSphere) (F-390)
Attachment 8 - TheraSphere Shipping Package Information Drawing
Attachment 9 - Revised Package Insert
Attachment 10 - Labeling: Page 7, Original Submission
Attachment 11 - TheraSphere Label Integrity Report
Attachment 12 - IS/TR 1190 F400/F390: Qualification Test Report of the F-400/F-390 Type 'A' Transport Package
Attachment 13 -Test Report: F390 Lead Pot and TheraSphere Acrylic Shield Drop Tests
Attachment 14 - PD99099003.08: Investigation Study Radiation Profile on a 20 GBq TheraSphere Dose Vial
Attachment 15 - Abstracted from: Operating Instructions, Model 471, General Purpose Survey Meter, Victoreen
Attachment 16 - Abstracted from: Operating and Instruction Manual, Johnson Model 2000W Extender, Wm. B. Johnson & Associates Inc.
Attachment 17 - Houle S. et al. Hepatocellular Carcinoma: Pilot Trial of Treatment with Y-90 Microspheres, Radiology, 172:No. 2, 857-860, 1989
Attachment 18 - Gordon, K. et al. Radiation Protection Aspects of Y-90 Radiotherapy for Malignant Tumors. Abstract Society of Nuclear Meeting, 1991.

Package Insert

TheraSphere® Yttrium-90 Glass Microspheres

Humanitarian Device.
Authorized by Federal Law for use in the treatment of patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training and experience.

DESCRIPTION

TheraSphere® consists of insoluble glass microspheres where yttrium-90 is an integral constituent of the glass [1]. The mean sphere diameter ranges from 20 to 30 μm. Each milligram contains between 22,000 and 73,000 microspheres. TheraSphere® is supplied in 0.05 mL of sterile, pyrogen-free water contained in a 0.3 mL vee-bottom vial secured within a 12 mm clear acrylic vial shield. A pre-assembled single use administration set is provided with each dose. TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi) and 20 GBq (540 mCi).

Yttrium-90, a pure beta emitter, decays to stable zirconium-90 with a physical half-life of 64.2 hours (2.68 days). The average energy of the beta emissions from yttrium-90 is 0.9367 MeV.

Following embolization of the yttrium-90 glass microspheres in tumorous liver tissue, the beta radiation emitted provides a therapeutic effect [2-6]. The spheres are delivered into the liver tumor through a catheter placed into the hepatic artery that supplies blood to the tumor. The spheres, being unable to pass through the vasculature of the liver due to arteriolar capillary blockade, are trapped in the tumor and exert a local radiotherapeutic effect with some concurrent damage to surrounding normal liver tissue [7-14].

INDICATION

TheraSphere® is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic arterial catheters.

CONTRAINDICATIONS

The use of TheraSphere® is contraindicated in patients:

- whose Tc-99 MAA hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract which cannot be corrected by angiographic techniques (see Item 1 under **INDIVIDUALIZATION OF TREATMENT**);
- who show shunting of blood to the lungs which could result in delivery of greater than 16.5 mCi of radiation to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment (see Item 2 under **INDIVIDUALIZATION OF TREATMENT**);
- in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities, bleeding diathesis, or portal vein thrombosis; and
- with severe liver dysfunction or pulmonary insufficiency.

PRECAUTIONS/WARNINGS

- Radioactive products should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.
- Adequate shielding and precautions for handling radioactive material must be maintained.
- As in the use of any radioactive material, care should be taken to insure minimum radiation exposure to the patient extraneous to the therapeutic objective and to insure minimum radiation exposure to workers and others in contact with the patient.
- Since adequate studies have not been performed in animals to determine whether this device affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this product should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.
- Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.
- Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately and the area monitored for contamination at the end of the procedure.
- The TheraSphere® dose vial is supplied secured within a clear acrylic vial shield to limit radiation exposure to personnel. The dose rate at the vial shield surface is still high enough to require caution including the use of tongs and a lead shielded container when possible. The vial should always be stored in a shielded location away from personnel.

ADVERSE REACTIONS

Based on clinical and preclinical animal experience with TheraSphere® and other yttrium-90 microspheres, certain adverse reactions have been identified [4-6, 15, 16, 17, 18]. Adverse events that occurred in the 100 Gy HCC (N=22), the Pilot HCC (N=9) [4], and the Mixed Neoplasia (N=4) [3, 11] studies are summarized by severity in Table 1.

The introduction of microspheres into the vasculature of the stomach, duodenum or other organs of the gastrointestinal tract can cause chronic pain, ulceration and bleeding. Microsphere shunting to the lungs can cause edema and fibrosis that may not be reversible. Extrahepatic shunting may be identified through the injection of Tc-99 MAA into the hepatic artery [19, 20]. Flow of radioactivity to the gastrointestinal tract may be avoided by the use of balloon catheterization or other angiographic techniques to block such flow [21]. The use of this product leads to irradiation of both tumorous and normal liver parenchyma. As a result patients with diseases which compromise the functioning of the non-tumorous liver parenchyma or with very small lesions scattered throughout the normal parenchyma may be at greater risk of liver function impairment.

Table 1
Incidence[a] of Treatment-Emergent Adverse Events From Three Studies[b] (N=35), SWOG Toxicity Grading System

Adverse Event	Mild	Moderate	Severe	Life Threatening	Lethal/Fatal	Total
Increased Transaminase (SGOT/SGPT)[c]	14 (40.0%)	14 (40.0%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	33 (94.3%)
Increased Alkaline Phosphatase	18 (51.4%)	9 (25.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	30 (85.7%)
Increased Lactic Dehydrogenase	19 (54.3%)	2 (5.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	24 (68.6%)
Increased Bilirubin	0 (0.0%)	9 (25.7%)	6 (17.1%)	4 (11.4%)	1 (2.9%)	20 (57.1%)
Abdominal Pain	6 (17.1%)	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	16 (45.7%)
Decreased Hemoglobin	8 (22.9%)	4 (11.4%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	15 (42.9%)
Nausea	9 (25.7%)	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	13 (37.1%)
Anorexia	11 (31.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Malaise/Fatigue/Lethargy	5 (14.3%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Other Pain[d]	5 (14.3%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Decreased White Blood Cell	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (28.6%)
Fever, Absence Infection	4 (11.4%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (25.7%)
Increased Creatinine	6 (17.1%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Increased Prothrombin Time	5 (14.3%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Edema	3 (8.6%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	7 (20.0%)
Weight Gain	5 (14.3%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (20.0%)
Gastric Ulcer	1 (2.9%)	0 (0.0%)	4 (11.4%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Other Liver[d]	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Vomiting	4 (11.4%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (17.1%)
Anxiety/Depression	4 (11.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Hemorrhage (Clinical)	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Other Gastrointestinal[d]	3 (8.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Decreased Platelet	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Cough	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Dyspnea	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Insomnia	4 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Weight Loss	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Constipation	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Diarrhea	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Hyponatremia	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Pneumonia	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)	3 (8.6%)
Sweats	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Dysrhythmia	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)
Headache	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
Infection	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)

Abbreviations: SWOG, Southwest Oncology Group; HCC, hepatocellular carcinoma; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

[a] For each patient, the highest severity of an adverse event was counted once. Adverse events that were reported by at least two patients in the total population are summarized.

[b] Studies: 100 Gy HCC (N=22), Pilot HCC (N=9), and Mixed Neoplasia (N=4).

[c] If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a 51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.

[d] Other pain included pain in back/lower back (3), epigastric (2), chest (1), legs (1), shoulder (1), stomach (1), toe (1), and musculoskeletal (1). Other liver included hepatitis (2) and ascites (4). Other gastrointestinal included abdominal discomfort (1), early satiety (1), heartburn (1), duodenal ulcer (1), and burping (1).

CLINICAL STUDIES

1. 100 Gy HCC Study

- *Objectives:* To define the activity of yttrium-90 microspheres given by hepatic artery infusion to a previously untreated patient with primary hepatocellular carcinoma (HCC); to evaluate the survival of patients treated with yttrium-90 microspheres; and to evaluate the toxicity of yttrium-90 microsphere therapy.
- *Study Design:* Patients with HCC were treated with a target dose of TheraSphere® of 100 Gy by injection through the hepatic artery. Patients underwent laboratory tests, history and physical examinations, and liver ultrasounds or computerized tomography (CT) scans for up to 2 years after treatment. Response duration was calculated from the

date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the Southwest Oncology Group (SWOG; Operations Office, San Antonio, TX) grading system (last revised 12/94), i.e., grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, and grade 5 = lethal/fatal. If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a 51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.

- *Patient Inclusion Criteria:* Presence of histologically confirmed unresectable HCC confined to the liver and at least one measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status 0-3; estimated life expectancy greater than 12 weeks; absolute granulocyte count 2.0 x 10^8/L or greater; platelet count 100 x 10^9/L or greater; prothrombin time (PT) and activated partial thromboplastin time within normal limits; bilirubin less than 1.5 x upper normal limit; serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase less than 5 x upper normal limit; normal pulmonary function defined as no more than 30% greater or less than the expected normal.
- *Study Population and Treatment Administration:* Twenty-two patients were treated. Two patients were excluded from the efficacy analysis due to an unconfirmed diagnosis of HCC. Twenty patients received one TheraSphere® treatment; two patients received a second TheraSphere® treatment based on the principle investigator's discretion. Nine patients were classified as Okuda stage I and 11 patients as Okuda stage II. The median activity administered was 3.9 GBq (range, 2.0 GBq to 9.2 GBq). The median liver dose was 104 Gy (range, 46 Gy to 145 Gy).
- *Efficacy Results:* One complete response and three partial responses were recorded, with one patient not being evaluable for response. The median survival was 378 days (95% CI, 209 to 719), with a minimum survival of 49 days and a maximum survival of 1,265 days.
- *Safety Results:* One patient suffered from a possible angiography contrast agent allergic reaction that was judged by investigator to be severe in nature. All 22 treated patients reported at least one treatment-emergent adverse event; however, the majority (85%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening, or lethal/fatal) adverse events were liver related (45%) and gastrointestinal (19%). Liver toxicities were primarily elevated enzymes during the week after treatment. The gastrointestinal toxicities included three ulcers, one ileus, and one nausea. Three patients died during the follow-up period. The deaths were attributed to hepatitis (death approximately 5 months after TheraSphere® treatment; judged as possibly related to TheraSphere®), gastric ulcer (death approximately 2 months after TheraSphere® treatment; judged as probably related to TheraSphere®), and radiation pneumonitis (death approximately 2 months after TheraSphere® treatment; judged as definitely related to TheraSphere® after the patient received an estimated dose of 56 Gy to the lungs as a result of pulmonary shunting).

2. Pilot HCC [4] and Mixed Neoplasia Studies [3, 11]

- *Objectives:* The objectives of the Pilot HCC study were to define the activity of yttrium-90 microspheres administered by hepatic arterial infusion to patients with HCC and to evaluate the toxicity of yttrium-90 microsphere therapy.
  The objectives of the Mixed Neoplasia study were to evaluate the toxicity of yttrium-90 microsphere therapy and to define, using escalating radiation doses, the maximum tolerated dose of yttrium-90 glass microspheres administered by hepatic arterial infusion that would be suitable for Phase II-III studies in a similar patient population.

- *Study Design:* Patients in the Pilot HCC study received TheraSphere® in an amount that was determined to deliver a radiation absorbed dose of approximately 50 Gy to the tumor. After treatment, patients underwent laboratory tests, history and physical examinations, and liver ultrasounds, radionuclide scans, or CT scans.
  The Mixed Neoplasia study was designed to treat patients with metastatic colonic carcinoma of the liver, carcinoid tumor metastatic to the liver, or primary hepatobilliary carcinoma. Patients received a single injection of TheraSphere® with an initial group of patients receiving a calculated radiation absorbed dose of 50 Gy to the liver; after determination of acceptable and reversible toxicity, a second group of patients received 75 Gy to the liver followed by a third group of patients who received 100 Gy to the liver. Patients underwent laboratory tests, history and physical examinations, and liver ultrasounds, radionuclide scans, or CT scans for up to 24 weeks after TheraSphere® treatment.
  For both studies, response duration was calculated from the date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the SWOG grading system (see above under 100 Gy HCC Study). If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a 51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.
- *Patient Inclusion Criteria:* Patients eligible for the Pilot HCC study had to have histologic or cytologic proof of primary HCC and the disease must have been measurable; ECOG performance status less than 3; estimated life expectancy greater than 12 weeks; absolute neutrophil count greater than 2,000 x 10^9/L; platelet count greater than 150 x 10^9/L; and normal pulmonary function defined as no more than 25% greater or less than the expected normal. Patients must have terminated any previous chemotherapy at least 4 weeks before entering the study and they must have recovered from all toxicity from the previous therapy.
  Patients eligible for the Mixed Neoplasia study had to have histological proof of surgically unresectable metastatic colonic carcinoma of the liver, carcinoid tumor metastatic to the liver, or primary hepatobiliary carcinoma; in addition, patients had to undergo hepatic arterial angiography or technetium-99m macroaggregated albumin (Tc-99 MAA) hepatic arterial perfusion to demonstrate that the hepatic tumor was vascular. Other eligibility criteria included Karnofsky performance status equal to or greater than 60; peripheral leukocyte count greater than 4,000/mm^3; granulocyte count greater than 2,000/mm^3; platelet count greater than 150,000/mm^3; serum albumin greater than 2.5 g/dL; bilirubin less than 2 mg/dL; SGOT less than 6 x normal; PT within 3 seconds of control (or correctable with Vitamin K to same); and serum creatinine less than 2.0 mg/dL. Patients also had to have a hepatic arterial perfusion scan using Tc-99 MAA or albumin microspheres showing complete perfusion of both lobes of the liver, an F (fraction of Tc-99 MAA activity observed in the lungs relative to the total Tc-99 MAA activity observed) times A (the yttrium-90 activity to be injected) product of 10 mCi or less, and no detectable Tc-99 MAA activity in the stomach and/or duodenum by gastric air contrast scan. Patients must have terminated any previous chemotherapy or non-hepatic radiation therapy at least 4 weeks before entering the study and they must have recovered from all toxicity from the previous therapy.
- *Study Population and Treatment Administration:* Thirteen patients, nine from the Pilot HCC study and four from the Mixed Neoplasia study, provide safety data. All 13 patients were treated once with TheraSphere®. The median activity administered was 2.6 GBq (range, 2.2 GBq to 6.6 GBq). The median liver dose was 74 Gy (range, 34 Gy to 105 Gy). Because of the dose escalation, seven patients received less than 80 Gy.

- *Efficacy Results:* Five patients were classified as having stable disease, four were classified as having progressive disease, and four were not evaluable for response. There were no survivors from these two studies and the median survival was 109 days (95% CI, 62 to 332) with a minimum survival of 15 days and a maximum survival of 1,557 days.
- *Safety Results:* All 13 treated patients reported at least one treatment-emergent adverse event; however, the majority (82%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening, or lethal/fatal) adverse events were liver related (43%). Liver toxicities were primarily due to elevated enzymes during the week after treatment. Among the serious adverse events, two patients also experienced gastric ulcers. Two patients died during the follow-up period. The deaths were attributed to elevated bilirubin (elevated before TheraSphere® treatment that increased in severity 2 days after treatment and continued until the patient's death 2 weeks later; judged as possibly related to TheraSphere®), and pneumonitis, (death approximately 6 weeks after TheraSphere® treatment; judged as possibly related to TheraSphere®).

INDIVIDUALIZATION OF TREATMENT

1. Gastroduodenal ulceration is a potential complication of inadvertent disposition of radioactive microspheres. It is likely that inadvertent deposition of yttrium-90 microspheres in the terminal gastric vascular bed reflects the backflow of microspheres during administration or shunting through aberrant small vessels within the cirrhotic liver or tumor. Although angiographic occlusion techniques and the use of vasoactive drugs may reduce gastrointestinal shunting, their effectiveness is uncertain.
2. In some patients, part of the hepatic arterial blood supply bypasses the capillary bed and flows directly to the venous system. This may be associated with pathologic abnormalities of the liver. For such patients, a fraction F of spheres injected into the hepatic artery will not be embolized in the liver but will flow to the heart and subsequently be deposited into the lungs. As the product of the bypass fraction, F, and the injected activity, A, increases the potential for delivering a damaging dose of radiation to the lungs increases. Consequently, it is essential that F be measured before use of this product. This can be done by injecting a tracer dose of Tc-99 MAA and observing with an Anger camera. The observed radiation from the lung field, divided by the total radiation observed by the camera is a measure of F. The product of F and A is then a measure of the activity that will be deposited into the lungs [22]. Based on clinical study experience [15, 16] with radioactive microspheres and TheraSphere® in HCC treatment, an upper limit of F x A of 610 MBq (16.5 mCi) is recommended. The estimated dose (Gy) to the lungs is equal to A (GBq) x F x 50, and assuming the total mass of both lungs to be 1 kg [23]; an upper limit of dose to the lungs from a single TheraSphere® treatment is 30 Gy.

HOW SUPPLIED

TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi), and 20 GBq (540 mCi). The dose is supplied in 0.05 mL of sterile, pyrogen-free water in a vee-bottom vial sealed within a 12 mm clear acrylic vial shield. Each dose is supplied with all the components required for administration, exclusive of items utilized in catheterization. The TheraSphere® dose and Administration Set should be stored at room temperature.

HANDLING AND STORAGE

Each dose vial of TheraSphere contains 5 to 20 GBqYttrium-90, a high-energy beta emitter. Even with low-density materials such as the product's lucite shield, the attenuation of beta particles gives rise to Bremsstrahlung which requires lead shielding. Users should avoid exposure by leaving the vial in the lucite product container, and by leaving the lucite container in the lead shield as much as possible. The use additional shielding is recommended. Finger ring dosimeters should be worn in the orientation most likely to record the highest exposure to the fingers

The product should not be removed from its lucite shield. It should be stored in the lead pot and lucite container in which it is packaged. The requirements of the applicable regulatory agency for safe handling and storage of radioactive materials should be consulted and must be adhered to.

INSTRUCTIONS FOR USE

Dosage and Administration

To correct for the physical decay of yttrium-90, the fractions that remain at selected time intervals from calibration are shown in Table 2.

Table 2
Yttrium-90 Physical Decay Table
Half-Life 64.2 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-4	1.044	24 (Day 1)	0.772	52	0.570
-2	1.022	26	0.755	54	0.558
0*	1.000	28	0.739	56	0.546
2	0.979	30	0.723	58	0.534
4	0.958	32	0.708	60	0.523
6	0.937	34	0.692	62	0.511
8	0.917	36	0.677	64	0.500
10	0.897	38	0.663	72 (Day 3)	0.459
12	0.878	40	0.649	96 (Day 4)	0.354
14	0.859	42	0.635	120 (Day 5)	0.273
16	0.841	44	0.622	144 (Day 6)	0.210
18	0.823	46	0.609	168 (Day 7)	0.162
20	0.806	48 (Day 2)	0.596		
22	0.789	50	0.583		

*Calibration Time

Preliminary Patient Evaluation

Prior to the administration of TheraSphere® the patient should undergo hepatic arterial catheterization using balloon catheterization or other appropriate angiographic techniques to prevent extrahepatic shunting [21]. Following the placement of the hepatic catheter, 75 MBq to 150 MBq (2 mCi to 4 mCi) of Tc-99 MAA is administered into the hepatic artery to determine the extent of A-V shunting to the lungs. Air contrast scintigraphic views of the stomach are also obtained to confirm the absence of gastric and duodenal flow. If such flow is present and cannot be corrected using established angiographic techniques the patient is disqualified from treatment. When the possibility of extrahepatic shunting has been evaluated and the patient deemed acceptable for treatment, TheraSphere® can be administered.

Calculation of Dose

The recommended dose to the liver is between 80 Gy to 150 Gy (8,000 rad to 15,000 rad). The amount of radioactivity required to deliver the desired dose to the liver may be calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{Liver Mass (Kg)}]}{50\,[1\text{-}F]},$$

where F is the fraction of injected activity deposited into the lungs as measured by Tc-99 MAA.

The liver volume and corresponding liver mass may be determined using CT or ultrasound scans.

If F is unknown, assume the upper limit of activity, which is 0.61 GBq, will be delivered to the lungs for the purpose of requisitioning TheraSphere®, and then using the Yttrium-90 Physical Decay Table (Table 2) to determine the appropriate time of injection. For determining the actual liver dose (Gy) delivered to the liver after injection, the following formula is used:

$$\textbf{Dose (Gy)} = 50\ \frac{\textbf{[Injected Activity (GBq)] [1 – F]}}{\textbf{Liver Mass (Kg)}}$$

The upper limit of injected activity shunted to the lungs is F x A = 0.61 GBq.

TheraSphere® Administration Set

The TheraSphere® Administration Set (Table 3 and Diagram 1) consists of one dose vial inlet set, one dose vial outlet set and one empty vial. Both the inlet set and the outlet set are made up of preassembled sterile, apyrogenic components as shown in the schematic diagram.

The dose vial inlet set, used to connect the fluid source to the TheraSphere® dose vial, consists of a fluid line (3), an inlet line (7) and a 5 mL pumping syringe (6), joined together via a red 3-way stopcock (4). The red stopcock is used to switch from the fluid line to the inlet line, so that fluid may be drawn into the syringe, then pumped through the inlet line and into the TheraSphere® dose vial.

The piercing pin (2) at the free end of the fluid line is used to connect the inlet set to the fluid source (1), usually a heparinized (100 U/mL) saline solution. The 20-gauge needle (9) at the free end of the inlet line is used to connect the inlet set to the TheraSphere® dose vial (10). A check valve (8) prevents spheres from flowing back into the inlet line. Consequently, the inlet set should not contain any radioactivity during a normal procedure.

The dose vial outlet set, used to connect the TheraSphere® dose vial to the patient catheter, consists of an outlet line (13) and a vent line (17) joined together via a blue 3-way stopcock (14). The patient catheter is connected to the free port (15) on the blue stopcock. The blue stopcock is used to switch from the vent line to the catheter (16), so that the system's lines can be properly vented before the TheraSphere® dose is administered. The 20-gauge needle (12) at the free end of the outlet line is used to connect the outlet set to the TheraSphere® dose vial. The dispensing pin and filter vent assembly (18) at the end of the vent line is used to connect the outlet set to the sterile empty vial (19). The empty vial is used to collect fluid and any spheres that may flush through during air venting. The filter vent in the dispensing pin prevents pressure buildup in the empty vial and also blocks any spheres from escaping. The dose vial outlet set, including the empty vial, may contain radioactivity at the end of the administration procedure. For added safety, the lead pot (20) used for shipping may be used to hold the empty vial during the procedure.

Throughout the administration procedure, the TheraSphere® dose vial (10) remains sealed within the clear acrylic vial shield (11) in which it was supplied. A removable plug at the top of the vial shield provides access to the septum of the TheraSphere® dose vial.

Administration Instructions

The entire contents of the TheraSphere® dose vial are administered to the patient.

The directions for administration should be followed to ensure accurate delivery of the calculated dose. Approximately 96% of the radioactivity in the TheraSphere® dose vial will be delivered to the patient using the recommended technique.

Assembly of Dose Vial Inlet Set (Table 3 and Diagram 1)

1. The fluid line (3) is connected to the fluid source (1) via the white piercing pin (2).
2. The 5 mL syringe (6) is connected to the free port (5) on the red 3-way stopcock (4).
3. The red stopcock is switched to the fluid line.
4. 5 mL of solution is drawn into the syringe from the fluid source.
5. The tamper-evident seal is removed from the top of the clear acrylic vial shield (11) exposing the top shielding plug which the seal had secured in place. The plug is now free and is removed by turning the vial shield over.
6. Once the plug has been removed, the vial shield is returned to its upright position and the septum of the TheraSphere® dose vial (10) is swabbed with alcohol.
7. The 20-gauge needle (9) at the free end of the inlet line (7) is carefully inserted through the center of the TheraSphere® dose vial septum and pushed to the bottom of the vee at the base of the vial.

Assembly of Dose Vial Outlet Set (Table 3 and Diagram 1)

8. The flip-off seal is removed from the empty vial (19).
9. The dispensing pin and filter vent assembly (18) on the free end of the vent line (17) is inserted through the septum of the empty vial.
10. The empty vial is placed in the lead pot used for shipping (20).
11. The 20-gauge needle (12) at the free end of the outlet line (13) is carefully pushed through the septum of the TheraSphere® dose vial until it is just visible below the level of the gold seal.

System Evacuation (Table 3 and Diagram 1)

12. The red stopcock is switched to the inlet line.
13. The blue stopcock (14) is switched to the vent line.

14. Fluid from the syringe is slowly forced through the inlet line, into the TheraSphere® dose vial, and out through the outlet and vent lines until all air is exhausted from the system and fluid has entered the empty vial.
NOTE: A low flow rate and gentle tapping of the TheraSphere® dose vial will reduce the possibility of premature introduction of spheres into the outlet line.

15. The outlet needle is pushed half way into the TheraSphere® dose vial. The purpose of this step is to eliminate the possibility of sweeping air that may be trapped near the top of the TheraSphere® dose vial into the catheter.

16. The red stopcock is switched to the fluid line and the syringe is refilled with 5 mL of solution.

17. The red stopcock is switched back to the inlet line.

TheraSphere® Administration (Table 3 and Diagram 1)

18. The patient catheter (16) is attached to the free port (15) on the blue stopcock.

19. The blue stopcock is switched to the catheter.

20. After verifying that both stopcocks are correctly positioned, the fluid in the syringe is expressed at a rate of approximately 1 mL per second. This flow rate will carry the spheres out of the TheraSphere® dose vial, through the outlet line, and into the catheter.

21. The red stopcock is switched to the fluid line and the syringe is refilled with 5 mL of solution.

22. The red stopcock is switched back to the inlet line and another 5 mL of solution is administered as in step 19.

Disassembly (Table 3 and Diagram 1)

23. The blue stopcock is switched to the vent line.

24. The catheter is disconnected from the blue stopcock.

25. The rest of the administration set is disassembled. The empty TheraSphere® dose vial, the dose vial outlet set and the catheter should be stored for decay or disposed of as radioactive waste.

RADIATION DOSIMETRY

The yttrium-90 in TheraSphere® is a constituent of an insoluble matrix thereby limiting irradiation to the immediate vicinity of the spheres. The average range of the radiation in tissue is 2.5 mm. One GBq (27 mCi) of yttrium-90 per kg of tissue gives an initial radiation dose of 13 Gy (1,297 rad) per day. The mean life of yttrium-90 is 3.85 days; thus, the radiation dose delivered by yttrium-90 over complete radioactive decay starting at an activity level of 1 GBq (27 mCi) per kg is 50 Gy (5,000 rad).

DISTRIBUTION

TheraSphere® is manufactured and distributed by MDS Nordion, Kanata, Ontario.

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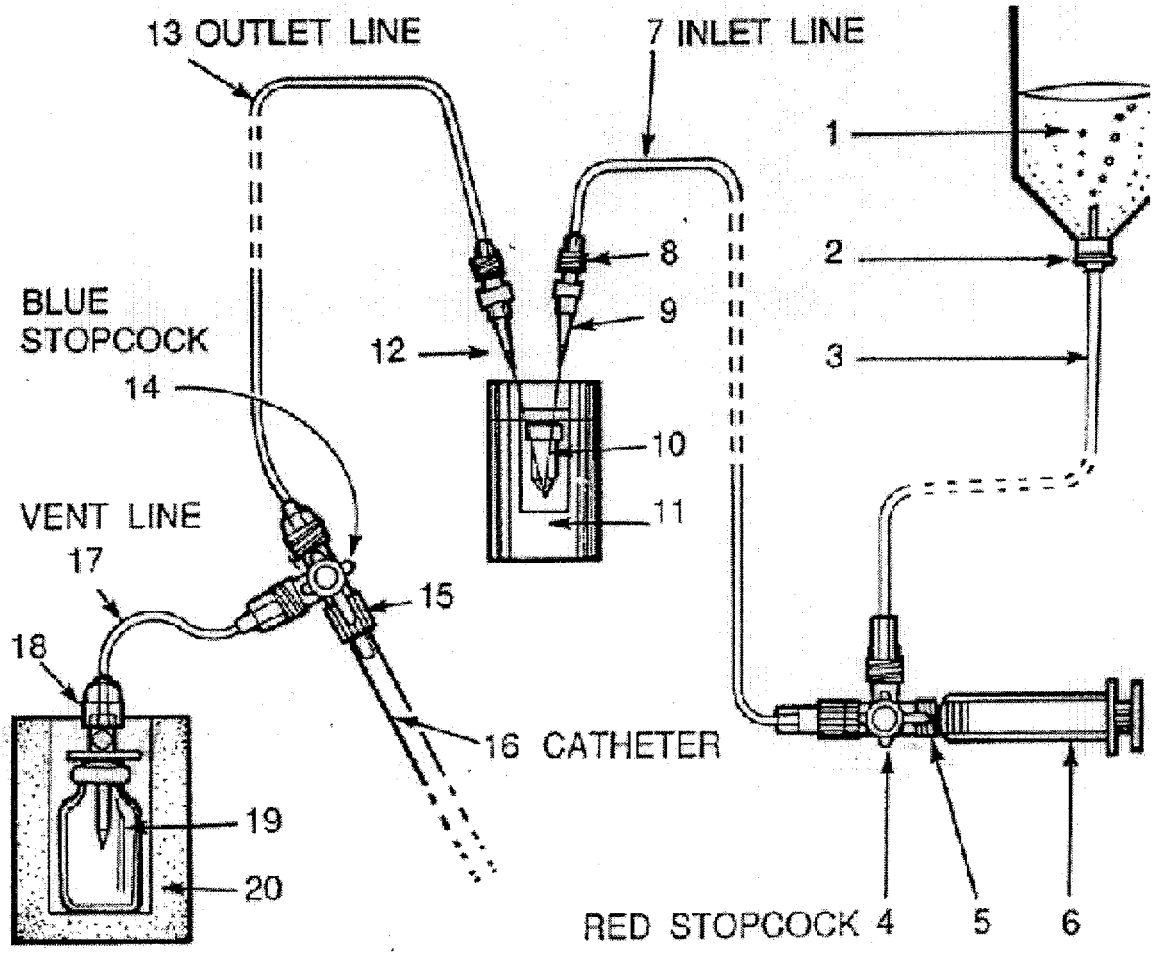
Table 3
TheraSphere® Administration Set - Contents

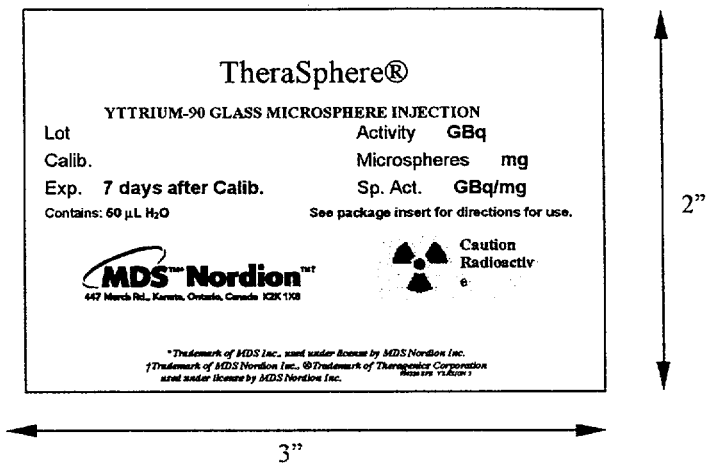
Drawing Number	Item
1	Fluid source
2	Piercing pin
3	Fluid line
4	Red 3-way stopcock
5	Free port on the red 3-way stopcock
6	5 mL syringe
7	Inlet line
8	Check valve
9	20-gauge needle at the free end of the inlet line
10	TheraSphere® dose vial
11	Acrylic vial shield
12	20 gauge needle at the free end of the outlet line
13	Outlet line
14	Blue 3-way stopcock
15	Free port on the blue stopcock
16	Catheter
17	Vent line
18	Filter vent assembly
19	Sterile empty vial
20	Lead pot

Diagram 1
TheraSphere® Administration Set



7. LABELING

Lead Pot/Lucite Shield Label



Once authorized, the following statement will be placed on the lead pot/lucite shield label:

Humanitarian device authorized by federal (USA) law for treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma who have appropriately positioned catheters.

Administration Set Label