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P-6

January 15, 2015

U.S. Nuclear Regulatory Commission
Region I
2100 Renaissance Boulevard, Suite 100
King of Prussia, PA 19406-2713

Re: NRC License 07-12153-02
Docket No. 030-01303

To Whom It May Concern:

This is a request for an expedited amendment to change the possession limits in Item 8F for the yttrium-90 resin SIR-Spheres® (NRC Registry of Sealed Sources and Devices Safety Evaluation of Sources Number MA-1229-D-101-S) from our current 108millicurie per vial and 500millicurie limit to 189millicurie (maximum) per vial and a 1000millicurie total limit. As per our e-mail discussion today, Sirtex did change MA-1229-D-101S to indicate 189millicuries. We were advised by the manufacturer's customer service department that we needed to make theses changes since the Y-90 SIR-sphere vials can arrive well before the calibration day/time due to production and shipping. The actual activity per milliliter at time of calibration will still be the same as listed in the manufacturer's package insert (3GBq in 5ml or 81mCi) and the prescribed dose delivered to the patient will still be based on that calibration point.

We have attached the memorandum from Sirtex Medical requesting the amendment change as well as the most recent package insert.

If you have any questions, or need any additional information, please contact me at by phone or e-mail address listed at the top of the first page.

Sincerely,

Joseph W. Vilani, MS, DABR
Radiation Safety Officer

Approved By,

Anthony Gialloreto, MS HCA, CNMT, RTN
Director, CCHS
Non-Invasive Services
For Dr. Patrick A. Grusenmeyer

JWV/jwv
Cc: File

ATTACHMENTS
1. Sirtex Memorandum of August 12, 2010
2. Package insert October 2011

585726
NMSS/RGN1 MATERIALS-002

**Sirtex Medical Inc.**
300 Unicorn Park Drive
Woburn, MA 01801 USA

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Fax: (978) 229-9585
Web: www.sirtex.com

# MEMORANDUM

**TO:** **ALL SIR-Spheres® microspheres Users, RSO's**
**FROM:** Linda Teigland
**Date:** August 12, 2010
**Subject:** License Amending Information

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In order to use our product, you will need to amend your Radioactive Materials License which will require the following information:

**Issuer:** The Commonwealth of Massachusetts, Radiation Control Program

**License No:** MA-1229-D-101-S

**Distributor:** Sirtex Wilmington LLC
16 Upton Drive, #2-4, Wilmington, MA 01887

**Sealed Source Model Designation:** Sirtex Medical Limited SIR-Spheres® microspheres

**Isotope:** Yttrium-90

**Minimum Activity:** 132 mCi per vial (Maximum activity 189 mCi per vial)

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1/27/12 revised corporate address

**Sirtex Medical Limited**
Level 33, 101 Miller Street, North Sydney NSW 2060
Australia
Tel: +61 2 9964 8400

**Sirtex Medical Inc**
300 Unicorn Park Drive, Woburn MA 01801USA
Telephone: 1 888 474 7839

SIRTeX

# *SIR-Spheres® microspheres*
## (Yttrium-90 Microspheres)

## 1. DESCRIPTION

SIR-Spheres microspheres consist of biocompatible microspheres containing yttrium-90 with a size between 20 and 60 microns in diameter. Yttrium-90 is a high-energy pure beta-emitting isotope with no primary gamma emission. The maximum energy of the beta particles is 2.27MeV with a mean of 0.93MeV. The maximum range of emissions in tissue is 11mm with a mean of 2.5mm. The half-life is 64.1 hours. In therapeutic use, requiring the isotope to decay to infinity, 94% of the radiation is delivered in 11 days. The average number of particles implanted is 30 – 60 x $10^6$. SIR-Spheres microspheres are a permanent implant.

SIR-Spheres microspheres are implanted into a hepatic tumor by injection into either the common hepatic artery or the right or left hepatic artery via the chemotherapy catheter port. The SIR-Spheres microspheres distribute non-uniformly in the liver, primarily due to the unique physiological characteristics of the hepatic arterial flow, the tumor to normal liver ratio of the tissue vascularity, and the size of the tumor. The tumor usually gets higher density per unit distribution of SIR-Spheres microspheres than the normal liver. The density of SIR-Spheres microspheres in the tumor can be as high as 5 to 6 times of the normal liver tissue. Once SIR-Spheres microspheres are implanted into the liver, they are not metabolized or excreted and they stay permanently in the liver. Each device is for single patient use.

## 2. INDICATIONS FOR USE

SIR-Spheres microspheres are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

## 3. CONTRAINDICATIONS

SIR-Spheres microspheres are contraindicated in patients who have:

- had previous external beam radiation therapy to the liver;
- ascites or are in clinical liver failure;
- markedly abnormal synthetic and excretory liver function tests (LFTs);
- greater than 20% lung shunting of the hepatic artery blood flow determined by Technetium MAA scan;
- pre-assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel;
- disseminated extra-hepatic malignant disease;
- been treated with capecitabine within the two previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres microspheres;
- portal vein thrombosis.

## 4. WARNINGS

- Inadvertent delivery of SIR-Spheres microspheres to the gastrointestinal tract or pancreas will cause acute abdominal pain, acute pancreatitis or peptic ulceration.
- High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis.
- Excessive radiation to the normal liver parenchyma may result in radiation hepatitis.
- Inadvertent delivery of SIR-Spheres microspheres to the gall bladder may result in cholecystitis.

## 5. PRECAUTIONS

- No studies have been done on the safety and effectiveness of this device in pregnant women, nursing mothers or children.
- Due to the radioactivity of this device and the significant consequences of misplacing the microspheres in situ, this product must be implanted by doctors with adequate training in the handling and implantation technique for this device.
- Sirtex recommends a SPECT scan of the upper abdomen be performed immediately after implantation of SIR-Spheres microspheres. The SPECT scan will detect the Bremsstrahlung radiation from the yttrium-90 to confirm placement of the microspheres in the liver.
- This product is radioactive. The use of this device is regulated under Title 10 of the Code of Federal Regulations Part 35. These regulations must be followed when handling this device.
- All persons handling, dispensing and implanting this device must be familiar with and abide by all Local, State and Federal regulatory requirements governing therapeutic radioactive materials. Accepted radiation protection techniques should be used to protect staff when handling both the isotope and the patient.
- Some patients may experience gastric problems following treatment but H-2 blocking agents may be used the day before implantation of SIR-Spheres microspheres and continued as needed to reduce gastric complications.
- Many patients may experience abdominal pain immediately after administration of SIR-Spheres microspheres and pain relief may be required.
- SIR-Spheres microspheres demonstrated a mild sensitization potential when tested dermally in an animal model.

## 6. CLINICAL TRIAL RESULTS

In a randomized, controlled clinical trial, a total of 70 patients were studied in two arms, 34 patients with FUDR chemotherapy (control group), and 36 patients with FUDR plus SIR-Spheres microspheres. The results are shown in the following tables.

**Table 1 – Tumor Response by Volume**

| Response | CR | PR | NC | PD | Others |
|---|---|---|---|---|---|
| FUDR only (N = 34) | 1 | 7 | 12 | 9 | 5 |
| FUDR + SIR-Spheres microspheres (N = 36)* | 2 | 16 | 10 | 5 | 3 |

* (P=0.033)

Tumor response was measured by two consecutive CT scans in a 3-month interval period.

CR = Complete Response, PR = Partial Response,
NC = No Change, PD = Progressive Disease,
Others = No follow up, or unmeasurable

Table 1 indicates that there is a statistically significant improvement of the tumor response rates (CR+PR) in the group treated with FUDR plus SIR-Spheres microspheres, when compared with the group treated with FUDR only.

**Table 2 – Time to First Progressive Disease in the Liver**

| | FUDR Only | FUDR + SIR-Spheres microspheres |
|---|---|---|
| Number of Patients | 34 | 36 |
| Mean Time in Days +/- SD* | 312 Days +/- 330 | 510 Days +/- 516 |
| Median Time in Days* | 233 Days | 366 Days |

*(P=0.05)

Progressive Disease was defined as more than 25 % increase of tumor volume, or development of new lesion(s) in the follow up CT scan, when compared to the pre-treatment CT scan.

Table 2 indicates that there is a statistically significant delay of time to progression of the disease in the group treated with FUDR plus SIR-Spheres microspheres, when compared with the group treated with FUDR only.

## 7. ADVERSE EVENTS

When the patient is treated with proper technique, without excessive radiation to any organ, the common adverse events after receiving the SIR-Spheres microspheres are fever, transient decrease of hemoglobin, mild to moderate abnormality of liver function tests (mild increase in SGOT, alkaline phosphatase, bilirubin), abdominal pain, nausea, vomiting, and diarrhea.

In the phase III randomized controlled clinical trial with 70 patients, there was a minimal increase of Grade 1 and 2 events, mostly transient abnormal LFTs and nausea and vomiting in the patients who received SIR-Spheres microspheres. There was no difference in the number of patients who developed Grade 3 and 4 adverse events between the two groups. No patient died due to the adverse events directly related to SIR-Spheres microspheres.

**Table 3 – Adverse Events**

| | Grade 1 and 2 | | Grade 3 and 4 | |
|---|---|---|---|---|
| Events | FUDR | FUDR + SIR-Spheres microspheres | FUDR | FUDR + SIR-Spheres microspheres |
| Hemoglobin | 4 | 5 | 1 | 0 |
| Bilirubin | 7 | 2 | 0 | 1 |
| AST (SGOT) | 110 | 109 | 14 | 7 |
| Alk. Phos. | 90 | 188 | 5 | 14 |
| Nausea/ Vomiting | 5 | 13 | 2 | 1 |
| Diarrhea | 6 | 3 | 1 | 0 |
| | | | | |
| Total | 222 | 320 | 23 | 23 |

The data are from a clinical trial with 34 patients on chemotherapy only, and 36 patients on chemotherapy plus SIR-Spheres microspheres.

**Potential Serious Adverse Events Due to High Radiation**

- **Acute pancreatitis** ---- causes immediate severe abdominal pain. Verify by SPECT imaging of the abdomen (Yttrium-90 Bremsstrahlung image) and test for serum amylase.
- **Radiation Pneumonitis** ---- causes excessive nonproductive cough. Verify by X-ray evidence of pneumonitis.
- **Acute Gastritis** ---- causes abdominal pain. Verify by standard methods to diagnosis gastric ulceration.
- **Radiation Hepatitis** ---- causes unexplained progressive deterioration of liver function. Verify by transcutaneous core biopsy of the liver.
- **Acute cholecystitis** ---- causes significant upper abdominal pain and may require cholecystectomy for resolution. Verify by appropriate imaging studies.

## 8. PATIENT SELECTION AND PRE-TREATMENT TESTING

- Patients are indicated for treatment with SIR-Spheres microspheres when the metastatic colorectal cancer in the liver is considered non-resectable. In any of the following circumstances, patients would generally be considered non-resectable:
  1. multiple liver metastases together with involvement of both lobes;
  2. tumor invasion of the hepatic confluence where the three hepatic veins enter the IVC such that none of the hepatic veins could be preserved if the metastases were resected;
  3. tumor invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken; and
  4. widespread metastases such that resection would require removal of more liver than is necessary to maintain life.
- Resectability may be evaluated via imaging with a triple phase contrast angio-portal CAT scan or MRI.

**Patient Tests Before Treatment with SIR-Spheres microspheres**

The following tests are recommended before treatment:

- A hepatic angiogram should be performed to establish arterial anatomy of the liver.
- A nuclear medicine break-through scan (Intrahepatic Technetium MAA Scan) to determine the percent lung shunting. If a port has been inserted, this test can be performed through the port.
- Serologic tests of liver function should be performed to determine the extent of liver function damage.

Appropriate imaging studies are recommended to determine the extent of disease. These may include chest x-ray, CT scan of chest and abdomen, abdominal ultrasound and a bone scan.

## 9. RADIATION SAFETY

The preparation and implant procedure must be regarded as being a potentially serious radiation hazard to the staff and a serious contamination hazard. Regulatory and local radiation usage guidelines should be followed concerning implantation and post-implantation care.

The following are sample measured thermoluminescent dosimetry (TLD) exposures to personnel.

**Table 4 – Exposure Dose Per Patient for Implant Preparation (Technologist)**

| | Trunk mSv (mrem) | Lens of the Eye mSv (mrem) | Hands mSv (mrem) |
|---|---|---|---|
| Shallow Dose (0.07mm) | 0.027 (2.7) | 0.026 (2.6) | 0.35 (35) |
| Deep Dose (10 mm) | 0.003 (0.3) | 0.004 (0.4) | |

Assuming handling of a 3 GBq device and dose preparation time of 30 minutes. TLDs were worn near the pelvis, on the shirt's lapel, and on the working finger.

**Table 5 – Exposure Dose Per Patient for Implant Procedure (Physician)**

| | Trunk mSv (mrem) | Lens of the Eye mSv (mrem) | Hands mSv (mrem) |
|---|---|---|---|
| Shallow Dose (0.07mm) | 0.038 (3.8) | 0.12 (12) | 0.32 (32) |
| Deep Dose (10 mm) | 0.004 (0.4) | 0.054 (5.4) | |

Assuming average patient dose of approximately 2 GBq and dose injection time of 20 minutes.

* SIR-Spheres is a Registered Trademark of Sirtex SIR-Spheres Pty Ltd

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**Post-Implant Exposure**

Exposure data from patients implanted with an average of 2.1GBq at approximately 5-6 hours post implantation at the following distances from the patient's abdomen:

| | |
|---|---|
| 0.25m | 18.8 µSv/hr |
| 0.5m | 9.2 µSv/hr |
| 1m | 1.5 µSv/hr |
| 2m | 0.4 µSv/hr |
| 4m | <0.1 µSv/hr |

(1mSv = 100 mrem)

## 10. HOW SUPPLIED

SIR-Spheres microspheres are provided in a vial with water for injection. Each vial contains 3GBq of yttrium-90 (at the time of calibration) in a total of 5 cc water for injection. Each vial contains 40 - 80 million microspheres. The vial is shipped within a 6.4mm thick, lead pot. The package consists of a crimp-sealed SIR-Spheres microspheres glass vial within a lead pot, and a package insert within Type A packing bucket.

The vial and its contents should be stored inside its transportation container at room temperature (15-25° C, 59-77° F).

The calibration date (for radioactive contents) and the expiration information are quoted on the vial label. The useful life of the SIR-Spheres microspheres is 24 hours from the time of calibration. The particle size has been validated before shipment, as 32.5µ +/- 2.5 µ. Less than 10% will be < 30 µ and > 35 µ.

# APPENDICES



## APPENDIX I – GENERAL INFORMATION

**Restricted to Accredited Facilities**

SIR-Spheres microspheres may only be dispatched to a duly licensed or accredited facility capable of handling therapeutic medical isotopes.

**Restricted to Licensed Physicians**

This device is licensed by the Agency for distribution to persons licensed pursuant to 105 CMR 120.500, 120.541 and 120.543 or under equivalent licenses of the Nuclear Regulatory Commission, an Agreement State, or a licensing State. Only doctors qualified and licensed under Title 10 Code of Federal Regulations Part 35 (Nuclear Regulatory Commission) may order and implant SIR-Spheres microspheres.

## APPENDIX II – DOSE PREPARATION PROCEDURE

- Unpack SIR-Spheres microspheres, leaving shipping vial in lead pot.
- Place on the bench top in a lead or acrylic shielded box if available.
- Remove the center of aluminum seal from sterile v-vial with forceps, and clean the septum with an alcohol swab.
- Place the v-vial in an empty lead pot (10 cm x 6 cm) for stability and shielding.
- Insert a short 25 gauge needle through the septum of the v-vial until it just pierces the septum to create a vent
- Remove the SIR-Spheres microspheres shipping vial from the lead pot and shake vigorously to disperse the SIR-Spheres microspheres.
- Using a dose calibrator, determine the activity in the shipping vial and return it to the lead pot.
- Remove partially the aluminum seal of the SIR-Spheres microspheres shipping vial, clean with alcohol swab.
- Insert a 25 gauge needle through the septum of the shipping vial to create a vent, ensuring the needle is well clear of the contents in the shipping vial.
- Use a shielded 5ml syringe with a 21 gauge hypodermic needle at least 50mm long to puncture the septum of the SIR-Spheres microspheres shipping vial, and quickly draw back and forth several times in order to mix the SIR-Spheres microspheres thoroughly.
- Quickly withdraw the pre-calculated patient radiation dose, and transfer into the vented v-vial in the other lead pot. Withdraw the required amount quickly before the contents of the shipping vial start to settle.
- Verify the patient dose in the v-vial by re-measuring the activity in the shipping vial with dose calibrator, and correct, if necessary.
- Put the v vial, containing the confirmed patient dose into the dedicated acrylic shield.

The patient dose is now ready for transport to the SIR-Spheres microspheres implantation room.

## APPENDIX III – CALCULATION OF INDIVIDUAL DOSE

There are generally two acceptable methods in calculating the individual patient dose; the partition model (individual dose calculation), and empirical model. The empirical model accepts the safety margins of the dose known from the previously published clinical data and chooses the most safe and effective dose from it. The empirical model has been used in the pivotal clinical trial of the SIR-Spheres microspheres.

The patient dose can be determined according to the following Table 1.

**Table 1 – The Recommended Patient Dose**

| The % Involvement by the Tumor in the Liver | Recommended Y-90 Dose* |
|---|---|
| > 50 % | 3.0 GBq |
| 25 % - 50 % | 2.5 GBq |
| < 25 % | 2.0 GBq |

**Caution:** The recommended implanted activities are specific to SIR-Spheres microspheres. They are not applicable and should not be extrapolated to other implanted Y-90 sources.

- When there is 10 % or more lung shunting, the patient dose would be further reduced, according to the following table 2.

**Table 2 – Dose Reduction Factors for Patients with Lung Shunting**

| % Lung Shunting | Reduction Factor |
|---|---|
| < 10 % | No reduction |
| 10 % - 15 % | 20 % reduction |
| 15 % - 20 % | 40 % reduction |
| > 20 % | No Treatment |

**Lung Shunt Calculation Procedure**

- Inject 4 mCi (150MBq) of Tc-99m MAA into the hepatic artery via a port or catheter;
- Use a large FOV gamma camera, and obtain anterior and posterior images of the chest and abdomen (with 700k to 1 million counts on abdomen, and the same count on the chest);
- Take right lateral abdomen, using same count;
- Draw ROI around the whole liver and the whole lung and get the total counts for the lung and the liver;
- Calculate the % shunt using following formula:

% Shunt = (Lung Counts / Liver Counts + Lung Counts) x 100

## APPENDIX IV – RADIATION DOSIMETRY

The radiation dosimetry of the SIR-Spheres microspheres can be a complex and difficult task due to the non-uniform distribution of the particles in the normal liver and the tumors. In general, 1 GBq (27 mCi) of Yttrium-90/kg of tissue provides 50 Gy of radiation dose.[1] However, because of the non-uniform distribution of the dose between the tumor and the normal liver tissue, a proportionally larger amount of radiation will be delivered to the tumor tissue, and less amount to the liver.

For example, a patient has a liver weighing 1500 g, and has two tumor nodules, a 4cm size tumor in the right lobe, and a 3cm size nodule in the left lobe. The post-injection images suggest that there is 5:1 density ratio for unit volume between the tumor and the liver. The patient received 2 GBq of SIR-Spheres microspheres. In such a case, the calculated radiation dose to the tumor is 294 Gy and the dose to the liver tissue is 58.5 Gy. The radiation dose for other organs would be minimal or negligible, except for the organs adjacent to the liver, such as the stomach, large intestine, gall bladder, and the lung. The radiation dose may increase significantly, when there is shunting of the arterial blood to the lung, stomach, or small intestine.

## APPENDIX V – TECHNIQUE FOR PERFORMING THE INTRA-HEPATIC TECHNETIUM MAA SCAN

| | |
|---|---|
| Purpose: | To assess arterial perfusion of the liver and the fraction of radiopharmaceutical tracer that will pass through the liver and lodge in the lungs |
| Agent: | Technetium-99 labeled MAA (Macro-Aggregated Albumin) |
| Dose: | 150MBq (4 mCi) |
| Equipment: | Any large FOV gamma camera |
| Administration: | The patient needs to have a surgically implanted port or trans-femoral catheter placed in the hepatic artery. The Technetium-99 labeled MAA is injected into the port or catheter. |
| Imaging: | The patient is positioned supine under the gamma camera and the images recorded<br>• Antorior and posterior images of abdomen and thorax<br>Collect 700k – 1000k cts for abdomen and same time for thorax<br>• Right lateral abdomen – same time acquisition as for anterior |
| Analysis: | Draw ROI around whole of liver and whole of lung fields. Calculate G mean for liver region and lung region<br>Calculate Lung/Liver ratio using the following formula<br>% lung shunting = (counts of total lung/counts of total lung plus counts of liver) x 100 |
| Interpretation: | If percent lung shunting is >10% then there is need for dose reduction of SIR-Spheres microspheres (*see Table 1 below*) |

**Table 1 – Dose Reduction Recommendations**

| Per Cent Lung Shunting | Activity of SIR-Spheres microspheres |
|---|---|
| < 10% | Deliver full amount of SIR-Spheres microspheres |
| 10% to 15% | Reduce amount of SIR-Spheres microspheres by 20% |
| 15% to 20% | Reduce amount of SIR-Spheres microspheres by 40% |
| > 20 % | Do not give SIR-Spheres microspheres |

## APPENDIX VI – CORRECTION FOR DECAY

The physical half-life of yttrium-90 is 64.1 hours. Radioactive decay factors should be applied at the time of patient dose preparation, in order to calculate the true value of radioactivity present.

**Table 1 – Decay Factors of Yttrium-90 SIR-Spheres microspheres**

| Hours | Decay Factor |
|---|---|
| 0.5 | 0.995 |
| 1 | 0.989 |
| 2 | 0.979 |
| 3 | 0.968 |
| 4 | 0.956 |
| 5 | 0.947 |
| 6 | 0.937 |
| 7 | 0.927 |
| 8 | 0.917 |
| 9 | 0.907 |
| 10 | 0.898 |
| 11 | 0.888 |
| 12 | 0.878 |
| 24 | 0.772 |
| 36 | 0.678 |
| 48 | 0.595 |
| 72 | 0.459 |

**Caution:** The time of the initial calibration must be converted to the user's local time.

[1] Russell, Carden, Herron: 'Dosimetry Calculations of Yttrium-90 used in the treatment of liver cancer.' Endocurietherapy/Hypertherm Oncol. 1988;4:171-186