Summary of Safety and Effectiveness Data

I. General Information

Device Generic Name: Radioactive Implant (Yttrium-90 microspheres)

Device Trade Name: SIR-Spheres®

Applicant's Name and Address: Sirtex Medical Inc.
c/o Matrix Medical Consulting Corp.
16835 West Bernardo Drive
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San Diego, CA 92127

Date of Panel Recommendation: November 6, 2000

Premarket Approval Application Number: P990065

Date of Good Manufacturing Practice Inspection: October 10 and 14, 2001

Date of Notice of Approval to Applicant: March 5, 2002

II. Indications for Use

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

III. Device Description

SIR-Spheres® is a device consisting of radioactive microspheres. It has two components, the microspheres and yttrium. The device is provided in water for injection to allow measurement of desired activity as a volume in a syringe.

How the device works
The active moiety of the device is the beta radiation emitted from the microspheres. Yttrium-90 is a beta emitter, to which hepatic tumors, as well as healthy liver tissue, are sensitive. The small penetration depth of these beta emissions into tissue limits the collateral damage that can occur with radiation sources implanted into tumors. The short half-life of 64 hours limits the radiation hazards to patients, staff and other caregivers, while providing a clinically appropriate dose of radiotherapy.

The properties of the beta radiation emitted from the microspheres are listed below.

Physical Properties of Yttrium-90
- Pure beta emitter with no associated primary gamma emission
- Energy of beta particles
  - Maximum 2.27MeV
  - Mean 0.93MeV

- Range
  - Maximum in air 9621mm
  - Maximum in tissue 11mm
  - Mean in air 3724mm
  - Mean in tissue 2.5mm
- Effective treatment time when isotope applied to infinity = 92.4 hours
- In a therapeutic application of decay to infinity, 94% of radiation is delivered in 11 days
- Fractional Bremsstrahlung yield
  - At maximal energy (2.27MeV)
    - In air 0.0089
    - In water 0.0081
    - In bone 0.0110
  - At mean energy (0.93MeV)
    - In air 0.0037
    - In water 0.0034
    - In bone 0.0043
- The fractional Bremsstrahlung yield may be roughly estimated from the following formula:

$$f = \frac{E_T.Z}{3000}$$

where f = fractional Bremsstrahlung
Z = atomic number
E_T= transitional energy of the beta particles

Principles of the operation of SIR-Spheres®

The device exploits the dominance of hepatic artery flow to tumor tissue. Normal hepatic tissue receives the majority of blood flow from the portal vein, with very little from the hepatic artery. Conversely, flow to tumor tissue is almost exclusively from the hepatic artery. By placing the microspheres via the hepatic artery, they are preferentially delivered to tumor tissue while sparing healthy tissue.

When yttrium-90 is implanted simultaneously or in close time relationship to either systemic or regional chemotherapy with suitable drugs, a synergy in tumor cell response occurs. This same synergy occurs in healthy tissue, thus it is important that microspheres be as contained as possible. The synergy continues until the emissions from the source have diminished. Placement of yttrium-90 into tumors, including those not readily detected before chemotherapy, can maximize response to treatment.

The total radioactivity required by a patient will be dependent on the extent and presentation of the tumor tissue, and is at the discretion of the treating physician. The time elapsed since calibration time and date will influence the volume or number of microspheres delivered to the patient. Currently, calibration is at 0900 hours Sydney, Australia time on day of calibration. Calculation of the remaining radioactivity at the time of patient treatment is via the decay curve for yttrium-90. The amount of radiation required is removed as a volume (in milliliters) for implantation into the patient. The calibration time also serves as a lockout time, before which the microspheres cannot be implanted. The time from shipping to calibration provides a window for product recall.

The device is presented as 2 vials, each containing 3 or 3.6 GBq±10% in 5mL at the time and date of calibration (as labeled). It carries a 24-hour expiration from time and date of calibration. This limit is imposed because, although the device is sterilized, it contains no preservative.

Patient Selection

Patient selection is critical in achieving a benefit from the use of SIR-Spheres®. Patients should be assessed before considering SIR-Spheres® to determine

- that they have metastatic colorectal cancer;
- if the tumor(s) are amenable to resection with curative intent; and
- if there are significant other sites of metastatic disease.

Liver cancer is considered 'resectable' if, in the opinion of an experienced hepato-biliary surgeon, all macroscopic evidence of tumor can be removed while maintaining sufficient normal hepatic parenchyma to sustain life. Determination of resectability should be via imaging with a triple-phase contrast angio-portal CAT scan or MRI.

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;
3. such that none of the hepatic veins could be preserved if the metastases were resected;
4. 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
5. widespread metastases, such that resection would leave less liver than is necessary to maintain life.

Patients who are considered candidates for treatment with SIR-Spheres® should be evaluated to determine the presence or absence of metastatic disease at extra-hepatic sites. As SIR-Spheres® is a form of loco-regional treatment only, the device has no beneficial effect on cancer at extra-hepatic sites. Therefore, when assessing patients for treatment with SIR-Spheres®, clinicians should determine if control of disease within the liver is likely to translate into patient benefit. If the liver cancer is the immediate life-threatening event, then treatment with SIR-Spheres® may still be indicated.

Renal and hepatic function should be assessed to determine the patient's ability to handle any concurrent chemotherapy and establish baseline liver function test (LFT) values. Seriously ill patients may not tolerate radiation therapy. SIR-Spheres® should not be implanted into patients with seriously compromised liver function or who have liver failure.

Patient Tests Before Treatment with SIR-Spheres®

Patients need both a hepatic angiogram and a nuclear medicine break-through scan. The former establishes the arterial anatomy of the liver while the later determines the percent lung shunting. Evaluation of patients for treatment should include appropriate tests to determine the extent of the disease. Appropriate tests might include chest X-ray, CT scan of chest and abdomen, abdominal ultrasound and bone scan. Serologic tests of liver function should be performed to determine the extent of compromise of liver function. Measurement of serologic tumor markers is useful as a baseline for subsequent monitoring of patients to determine response to treatment.

Restrictions on Use

SIR-Spheres® is a radioactive device and as such is subject to the provisions of Title 10 CFR Part 35. This restricts usage to facilities (medical institutions) and physicians duly qualified to handle therapeutic radiation. Only doctors qualified and licensed under Title 10 CFR Part 35 may implant

SIR-Spheres®. The sponsor has designed and will provide a training program to physicians for handling and implanting SIR-Spheres®. The company will restrict the sale of SIR-Spheres® to physicians who have undergone this training.

SIR-Spheres® is available only from Sirtex Medical Inc. (or its appointed representative) on receipt of a request from a licensed physician. Patients are not able to purchase SIR-Spheres®. A medical institution may place an order on behalf of a doctor.

SIR-Spheres® may only be dispatched to a duly licensed or accredited facility capable of handling therapeutic medical isotopes. Such a facility may be a hospital with a medical physics department or a radioisotope dispensing facility.

IV. Contraindications

SIR-Spheres® is 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,
- 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®,
- portal vein thrombosis.

V. Warnings

- Inadvertent delivery of SIR-Spheres® 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.

VI. 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 Medical Inc recommends a SPECT scan of the upper abdomen be performed immediately after implantation of SIR-Spheres®. 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 Title10 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® and continued as needed to reduce gastric complications.
- Many patients may experience abdominal pain immediately after administration of SIR-Spheres® and pain relief may be required.
- SIR-Spheres® demonstrated a mild sensitization potential when tested dermally in an animal model.

VII. Alternative Practices and Procedures

Hepatic Perfusion Chemotherapy without Sir-Spheres®

This modality restricts chemotherapy to the liver. The drugs most commonly used are either floxuridine or 5-fluorouracil. This therapy requires the placement of an internal pump, or alternatively, a port to accommodate an external pump to deliver the chemotherapy. The pump is loaded at regular intervals and delivers the drug over an extended period in monthly cycles.

Hepatic artery chemotherapy is generally only indicated for patients with liver metastases from the gastrointestinal tract and when the liver is the only site of disease. Response rates are higher than for systemic chemotherapy and there is probably a small advantage for those patients with disease limited to the liver.

VIII. Marketing History

This device was approved for marketing by the Therapeutic Goods Administration in Australia in February 1998. This device is approved for unrestricted sale in Australia (within radiation safety guidelines) and for export to nine other countries, these being Hong Kong, New Zealand, Philippines, Thailand, South Korea, Taiwan, Japan, Singapore and Canada. There are no further regulatory restrictions on the sale of the product in Hong Kong, Philippines, Thailand or New Zealand, other than radiation safety practices. SIR-Spheres® has not been withdrawn from marketing for any reason relating to the safety or effectiveness of the device.

IX. Adverse Effects of the Device on Health

The following toxicity events were observed during the randomized clinical trial with 34 patients on intra-hepatic chemotherapy alone and 36 patients on intra-hepatic chemotherapy plus SIR-Spheres®.

Adverse Events

	Grade 1 and 2		Grade 3 and 4	
Events	**FUDR**	**FUDR + SIR-Spheres®**	**FUDR**	**FUDR+ SIR-Spheres®**
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

Adverse events experienced in the first two months of treatment were analyzed separately and are presented above. This window was selected because the acute effects of yttrium-90 will have occurred and any longer term events (such as, for example, radiation pneumonitis) should be evident by this time.

Eleven patients who received SIR-Spheres® and chemotherapy experienced Grade 3 or 4 adverse events in the first two months post-treatment compared with five patients receiving chemotherapy alone. However, the type of events and grades (severity) of events experienced by patients on both arms were similar. The majority of events were grade 1 or 2 toxicity, which are not clinically significant in this patient group. These toxicity data are captured in the above table.

In the three cases where SIR-Spheres® and chemotherapy together were considered the cause, two were grade 1 nausea and one was pancreatitis. This was one of two grade three events on the SIR-Spheres® plus chemotherapy arm, the other being nausea and vomiting attributed to chemotherapy. The patient who experience acute pancreatitis had uncontrolled mild diabetes before treatment which was exacerbated by the pancreatitis. The pancreatitis was brought under control with medication. The pancreatitis settled rapidly with conservative management.

Virtually all patients develop a post-operative fever that starts immediately after implantation of SIR-Spheres® and can last from a few days to a week. The fever does not necessarily indicate sepsis but may be related to the embolic effect of the microspheres and the acute toxic effects on the tumor.

Many patients experience abdominal pain immediately after administration of SIR-Spheres® and may need pain relief with narcotic analgesia. The pain generally subsides within an hour or so, but patients may require oral analgesia for up to several days.

Many patients will experience nausea that may last up to several weeks and this may occasionally be severe enough to require anti-emetic medication, which should be continued until the symptoms subside.

Potential Adverse Events

Immediate severe unremitting pain post procedure could suggest that the microspheres have lodged in a site such as the pancreas and should prompt investigations to determine whether microspheres have lodged in an organ other than the liver. An yttrium-90 nuclear scan will determine if the microspheres

have lodged in the pancreas or other organs. Diagnosis of the pain must include other tests such as serum amylase. Treatment of the affected organ requires standard medical practice.

The development of acute peptic ulceration is suggested by the recognized symptoms of ulcer disease and diagnosed by endoscopy. Treatment is the same as for any cause of acute peptic ulceration.

High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis. This may be suspected if patients develop a non-productive cough several days or weeks after the implantation of SIR-Spheres® and is diagnosed by chest X-ray. Patients may be treated with systemic corticosteroids and supportive care until the disease has subsided.

Excessive radiation to the normal liver parenchyma may result in radiation hepatitis. This can be difficult to diagnose, and may appear many weeks after the implantation of SIR-Spheres®. It is suspected if there is unexplained progressive deterioration in liver function. The diagnosis can be confirmed by histologic examination of core liver biopsy. If the diagnosis is suspected or proven then patients should be treated with appropriate therapy and supportive care.

This device is permanently implanted and cannot be retrieved. There is no evidence to date that the decayed microspheres remaining in the tumor or liver cause adverse reactions.

X. Summary of Pre-clinical Studies

The safety of the microspheres for tissue implantation (using non-radioactive yttrium microspheres) was investigated using seven studies (three animal studies and four in vitro studies). All studies were conducted using Good Laboratory Practice in compliance with United Kingdom Regulations 1997 (SI 1997 N0 654) that are in turn in compliance with the OECD principles of GLP.

Study 1 Mutation capacity (bacterial reverse mutation test)
The objective of this study was to test the ability of SIR-Spheres® in vivo to induce mutations in four histidine-dependent auxotrophic mutants of S. typhimurium, strains TA1535, TA1537, TA98 and TA100 and one tryptophan-dependent auxotrophic mutant of E. coli, strain WP2 uvrA. No statistically significant increase in revertant numbers was observed for any strain at any dose with or without S-9, in either experiment. Yttrium microspheres were not mutagenic under the conditions of this test.

Study 2 Cytogenetic activity (in vitro mammalian cell cytogenetic test in Chinese hamster ovary cells)
This study was to assess the mutagenic activity of SIR-Spheres® by its ability to cause structural damage to chromosomes. There were some small but statistically significant increases in the aberrations after exposure to the microspheres. These were not consistent between cultures or experiments and were within the background range for this cell line. Yttrium microspheres do not show clastogenic activity under the conditions of this test.

Study 3 Haemocompatibility (tested to ISO 10993)
This study was intended to determine if endogenous or extraneous substances present in or on SIR-Spheres®, as tested in vitro, have hemolytic activity against human erythrocytes. Under the experimental conditions employed, the yttrium microspheres demonstrated no hemolytic activity against human erythrocytes. The suspending water, as expected, caused hemolysis in preclinical testing.

Study 4 Cytotoxicity (in vitro cytotoxicity to ISO 10993 Part 5)
This study was to evaluate the toxicity, in vitro, of leachable endogenous or extraneous substances present on or in SIR-Spheres®. The yttrium microspheres did not cause any changes in cell morphology and did not have any cytotoxic capacity.

Study 5 Sensitization (maximum sensitization test in the guinea pig ISO 10993-10)
This study evaluated the potential of SIR-Spheres® to cause a delayed dermal hypersensitivity/Type IV immune response in guinea pigs. The procedures used were based on the methods described in the document ISO 10993-10 Biological Evaluation of Medical Devices: Test for Irritation and Sensitization of March 1995. Weak positive responses in the test group were observed. These are indicative of a delayed dermal hypersensitivity immune response according to the criteria described in ISO 10993. Therefore, yttrium microspheres can be considered a mild sensitizer under the conditions of this test.

Study 6 Tissue toxicity (intracutaneous injection test in the rabbit ISO 10993-10)
This study was to assess the potential of Sir-Spheres® to produce irritation following intracutaneous injection. The methods used were based on those described in ISO 10993-10 Biological Evaluation of Medical Devices: Tests for Irritation and Sensitization, March 1995. Yttrium microspheres gave a mild irritant dermal reaction under the conditions of this test due to the alkaline nature of the yttrium test material.

Study 7 Systemic toxicity (systemic injection test in the mouse ISO 10993-11 (modified)
This study evaluated systemic responses to extracts of SIR-Spheres® following intravenous or intraperitoneal injection into mice. The procedures used were based on the methods described in ISO 10993-11 Biological Evaluation of Medical Devices – Part 11: tests for systemic toxicity and the United States Pharmacopoeia 23, 1995 for the assessment of biological reactivity, in vivo, section 88 page 1699. Under the conditions of this study, yttrium microspheres did not produce any systemic toxicity.

XI. Summary of Clinical Studies

Trial Design
A randomized prospective trial was designed to compare the benefit of adding a single implantation of SIR-Spheres® to a regimen of intra-hepatic artery chemotherapy with FUDR for patients with advanced non-resectable liver metastases from primary adenocarcinoma of the colorectum.

Subject Selection Inclusion and Exclusion Criteria
All patients had advanced non-resectable liver metastases from adenocarcinoma of the large bowel that had been completely resected and an acceptable performance status. Patients with distant extra-hepatic metastases or previous radiation treatment to the liver were excluded, but previous chemotherapy was allowed. Patients underwent surgical implantation of a hepatic artery port for delivery of the treatment specified by the protocol.

Treatment
Patients eligible for trial entry were stratified according to the size of tumor within the liver and then randomized to a control or investigational treatment arm. Treatment for patients randomized into the Control Arm consisted of ongoing cycles of continuous infusion hepatic artery chemotherapy with Floxuridine (0.3mg/kg/day) in 12-day cycles and repeated at 4 weekly intervals for 18 months. The Investigational Arm consisted of the same chemotherapy with the addition of a single implantation of SIR-Spheres®.

Study Population
Patients were treated at two major teaching hospitals in Western Australia. Seventy-four patients entered the trial of which 70 were eligible for analysis. The population was 77% male with an average age of approximately 60 years. The majority of patients had primary cancer arising from the colon (91% on the Control Arm and 78% on the Investigational Arm) with remainder having primary rectal cancer. The two arms were matched for patient and tumor characteristics.

Seventy-one percent of patients on the Control Arm and 67% of patients on the Investigational Arm had involvement of regional draining bowel nodes. Just over 70% of patients on both arms had moderately differentiated primary bowel cancer. About 70% of patients on each arm had less than 25% of liver replacement by tumor, and a further 25% had between 25 and 50%. The remainder had greater than 50% liver replacement with tumor. Fifteen percent of patients on each arm had had previous chemotherapy for their liver metastases.

The lead-time from diagnosis of liver metastases until randomization was an average of 51 days for the Control Arm and 56 days for the Investigational Arm. For the duration of protocol treatment, patients on the Control Arm averaged 1822mg per day of FUDR compared with 1863mg per day for patients on the Investigational Arm.

Study Period
The study period was from trial entry until death. This period included a Protocol Treatment period (the time from start of treatment conforming to the trial protocol until there was evidence of disease progression in the liver, development of cancer at non-hepatic sites, or failure of the port). This was followed by a non-protocol period that continued until date of death or last known to be alive.

Safety and Effectiveness Data

1. Effectiveness Data
   Patients were evaluated for Response and Progression by blinded serial measurement of changes in:
   - i) Tumor Volume - using two independent medical reviewers (JA, PM) and an average of all operators
   - ii) Cross Sectional Tumor Areas - using a medical reviewer (BG)
   - iii) Serum Carcinoembryonic Antigen (CEA).

The following tables summarize the primary and secondary findings from this trial. Data is provided for each criterion that measured an outcome for the trial as recorded by each independent operator. It should be noted that the study failed to achieve the primary objectives of the study. No difference was seen in the overall survival nor in the quality of life for these patients.

All p-values in the following Tables are derived from 2-tailed tests of significance. Response in the following table includes both complete response (disappearance of all tumor on two successive CAT scans not less than 4 weeks apart) and partial response (a 50% or more objectively measured decrease in tumor size on two successive CAT scans not less than 4 weeks apart).

Primary Findings

Parameter	Control Arm Chemotherapy	Investigational Arm SIRT+Chemotherapy	p-value
VIII. Response (Complete + Partial Responses)			
Tumor Volume (JA)	9 patients	19 patients	p = 0.053 (e) p = 0.102 (a)
Tumor Volume (PM)	9 patients	19 patients	p = 0.020 (e) p = 0.039 (a)
Tumor Volume (Averaged)	8 patients	18 patients	p = 0.033 (e) p = 0.064 (a)
Tumor Area	6 patients	16 patients	p = 0.011 (e) p = 0.023 (a)
CEA	16 patients	26 patients (e) 29 patients (a)	p = 0.004 (e) p = 0.002 (a)
Duration of Response (only patients with a 'Response' are included in this Table)			
Tumor Volume (JA)	314 days (mean) 315 days (median)	593 days (mean) 406 days (median	p = 0.16 (a)
Tumor Volume (PM)	454 days (mean) 315 days (median)	505 days (mean) 406 days (median)	p = 0.44 (a)
Tumor Volume (Averaged)	511 days (mean) 365 days (median)	513 days (mean) 357 days (median)	p = 0.89 (a)
Tumor Area	386 days (mean) 388 days (median)	610 days (mean) 557 days (median)	p = 0.31 (a)
CEA	207 days (mean) 169 days(median)	307 days (mean) 182 days (median)	p = 0.96 (a)
Time to First Progression in the Liver (all patients)			
Tumor Volume (JA)	244 days (mean) 222 days (median)	459 days (mean) 321 days (median)	p = 0.003 (a)
Tumor Volume (PM)	291 days (mean) 203 days (median)	506 days (mean) 361 days (median)	p = 0.017 (a)
Tumor Volume (Averaged)	306 days (mean) 230 days (median)	482 days (mean) 324 days (median)	p = 0.08 (a)
	312 days (mean) 233 days (median)	510 days (mean) 366 days (median)	P = 0.043 (e)
Cross Sectional Tumor Area	300 days (mean) 287 days (median)	563 days (mean) 469 days (median)	p = 0.001 (a)
CEA (may not be Progression in the liver)	195 days (mean) 174 days (median)	328 days (mean) 201 days (median)	p = 0.064 (a)
Survival			
Kaplan-Meier Analysis	550 days (mean) (a) 477days (median) (a)	684 days (mean) (a) 501 days (median) (a)	p = 0.20
	563 days (mean) (e) 487 days (median)(e)	716 days (mean) (e) 519 days (median) (e)	p = 0.18
Time Dependent Cox Regression Analysis	< 15 months (e) > 15 months (e)		p = 0.97 p = 0.075
Hazard Ratios	1.29 (all patients) unadjusted for strata		p = 0.3
	1.38 (all patients) adjusted for strata		p = 0.2
	1.33 (eligible patients) unadjusted for strata		P = 0.25
	1.41 (eligible patients) adjusted for strata		p = 0.18

- (e) = eligible patients, (a) = all patients SIRT = Selective Internal Radiation Therapy

Secondary Findings

Parameter	Control Arm Chemotherapy	Investigational Arm Chemotherapy + SIRT	p-value
Duration of Protocol Chemotherapy	206 days (mean) 151 days (median)	230 days (mean) 208 days (median)	p = 0.52 (a)
Survival After Protocol Treatment	328 days (mean) 283 days (median)	439 days (mean) 289 days (median)	p = 0.38 (a)
Time to Treatment Failure	235 days (mean) 183 days (median)	372 days (mean) 216 days (median)	p = 0.297 (a)
	240 days (mean) 187 days (median)	393 days (mean) 240 days (median)	p = 0.25 (e)
Size of Regression (all patients)			
Tumor Volume (JA)	68.1% (mean) 73.7% (median)	78.4% (mean) 83.4% (median)	p = 0.38 (e)
	68.1% (mean) 73.7 (median)	76.1% (mean) 82.7% (median)	p = 0.53 (a)
Tumor Volume (PM)	70.9% (mean) 75.3% (median)	67.7% (mean) 70% (median)	p = 0.88 (e)
	70.9% (mean) 75.3% (median)	66.8% (mean) 70% (median)	p = 0.77 (a)
Tumor Volume (averaged)	65.8% (mean) 64% (median)	71% (mean) 74.2% (median)	p = 0.54 (e)
	65.8% (mean) 64% (median)	69.6% (mean) 73.6% (median)	p = 0.65 (a)
Tumor Area	53% (mean) 46% (median)	67% (mean) 72% (median	p = 0.11 (e)
	53% (mean) 46% (median)	66% (mean) 71% (median)	p = 0.11 (a)
CEA	61% (mean) 68.5% (median)	82% (mean) 85.7% (median)	p = 0.008 (e)
	61% (mean) 68.5% (median)	82.7% (mean) 87.8% (median)	p = 0.005 (a)
Time to First Response (for patients with 'Response')			
Volume (JA)	128 days (mean) 124 days (median)	135 days (mean) 120 days (median)	p = 0.71 (a)
Volume (PM)	134 days (mean) 124 days (median)	127 days (mean) 124 days (median)	p = 0.88 (a)
Volume (averaged)	142 days (mean) 131 days (median)	126 days (mean) 121 days (median)	p = 0.54 (a)
Area	151 days (mean) 132 days (median)	116 days (mean) 121 days (median)	p = 0.28 (a)
CEA	60 days (mean) 56 days (median)	60 days (mean) 50 days (median)	p = 0.66 (e)
	60 days (mean) 56 days (median)	58 days (mean) 49 days (median)	p = 0.51 (a)
Toxicity and Adverse Events			
Grade 3 & 4 Events	23 (e) 26 (a)	22 (a)	

Events/Cycle (all grades)	0.9	1.1	
Serious Adverse Events	14	13	

2. Safety Data

Adverse Reactions and Complications

There were two groups of adverse reactions: toxicity from the chemotherapy, with or without the addition of the device; and serious events requiring hospitalization. The toxicity profile for both arms of the study was similar in profile and the number of events. Serious toxicity (grade 3 or 4 on the Union Internationale Contre le Cancer scale) occurred infrequently, in the order of about 20 events on each arm over the duration of protocol chemotherapy. This represents about 0.08 high-grade toxicity events per treatment cycles for the control arm and 0.07 for the Investigational Arm. There was approximately one toxic event per cycle of treatment administered on both arms of the study when all grades of toxicity were considered.

The serious adverse event rate was also similar on both arms of the treatment, and consisted primarily of complications related to the implanted port required for the administration of the intra-hepatic artery chemotherapy. This same port was utilized to implant the device. Fourteen serious events occurred in the Control Arm and 13 in the Investigational Arm. Of these, 9 and 10 respectively were related to port management. For the remainder, it was difficult to discern if they were disease or treatment related.

Serious Adverse Events Occurring during Protocol Chemotherapy

Event	Chemotherapy only Arm	Chemotherapy + SIRT Arm
Removal of port for any reason	1	2
Resiting of port for any reason	1	6
Infection or blockage of port not leading to removal or resiting	4	2
Other port related events	3	0
Fever of uncertain origin	2	1
GI symptoms of uncertain origin	2	1
Surgical complications	1	1
Total	14	13

Patient Discontinuation

The device is permanently implanted and cannot be retrieved unless the tumors become suitable for resection at some later stage, which occurs for very few patients in this target population. It was implanted only once at the start of protocol treatment for patients on the Investigational Arm. The radiation emitted from the device has a half-life of 64.1 hours, thus over a period of two weeks over 97% of the effective ionizing radiation has been delivered. Thereafter, protocol treatment was the same on both arms, consisting of regional intra-hepatic artery chemotherapy for 12 days per month for a maximum of 18 cycles. As such, patients could not discontinue use of the device, only use of the ensuing chemotherapy.

Patients on both arms discontinued protocol chemotherapy when they completed the 18 cycles, or required a change of therapy for a variety of reasons. More patients on the Investigational Arm completed the full 18-cycle protocol (7 vs. 1), while more patients on the Control Arm discontinued treatment due to progressive disease in the liver (13 vs. 6). A similar number of patients discontinued protocol therapy due to the development of extra-hepatic metastases (35% on the Control Arm and 36% on the Investigational Arm). Patients were followed after introduction of non-protocol chemotherapy until death or last known to be alive.

Device Failures and Replacements

Device failure occurs if the isotope leaches from the microsphere and deposits in bone. SIR-Spheres® has leaching of less than 0.1% as determined by Sirtex Medical, Inc. This represents the only potential failure point for this device. In addition, monthly blood tests indicated that no myelosuppression occurred, corroborating the lack of leaching.

Statement on Gender Bias

Patients treated with SIR-Spheres® were selected for treatment on the basis of selection criteria as previously outlined. Patients were sequentially enrolled into the trial on the basis of inclusion criteria, and gender was not a randomization stratum nor deliberately balanced. No significant differences were found between males and females when tested by hazard ratios for time to treatment failure, time to disease progression and survival, however, the majority of patients were male.

XII. Conclusions Drawn from Nonclinical and Clinical Studies

For patients with advanced colorectal liver metastases, the addition of a single treatment of SIR-Spheres® to intra-hepatic artery chemotherapy with FUDR significantly increases both the Tumor Response Rate and Time to Disease Progression.

SIR-Spheres® is safe when correctly implanted into tissues, and does not leach toxic substances into the systemic circulation.

The microspheres are a mild dermal sensitizer.

The most significant potential adverse events are radiation hepatitis and pneumonitis. While uncommon, these are potentially life threatening.

XIII. Panel Recommendation

The Radiological Devices Panel met on November 6, 2000 to discuss this PMA for SIR-Spheres®. Following a thorough discussion of the issues, the Panel unanimously recommended approval of the PMA with conditions.

The specific conditions recommended were the following:

1. Revise the labeling to include dosimetry information, radiation protection information for the users and improved patient information.
2. Require appropriate training for users.
3. Revise the Indications for Use to specify that the device is for metastatic colorectal cancer.
4. Require post-approval observational studies of safety and effectiveness to be designed with the FDA.

XIV. CRDH Decision

On the basis of the pivotal clinical study, CDRH concluded that the Indication for Use of this device should be limited to use with FUDR, the chemotherapy agent used in the study. CDRH considered the need for the panel-recommended post-approval study and concluded that a post-approval study is not required. The company has provided adequate data to substantiate the safety and effectiveness of its device for the approved indications for use. The bases for this conclusion are as follows:

1. The primary study end-points established by the applicant were 1) increased survival and 2) improved quality of life. Neither end-point was demonstrated in a statistically valid manner, although the data suggested a trend toward longer survival and also showed that quality of life did not worsen.

2. CDRH concluded that increased survival and improved quality of life (QOL) measures are not necessary end-points for this PMA. Survival is determined not only by metastases in the liver (the treated organ), but also by metastases in other, non-treated organs. Therefore, treating the liver may have little effect on the survival of the patient. QOL would not reasonably be expected to improve because patients in both arms of the study were treated with chemotherapy and suffered its side effects.

3. The secondary end-points established by the applicant were 1) tumor regression and 2) increased time to tumor progression. Given that SIR-Spheres® targets only the liver, these end-points are more appropriate as primary end-points. The study showed statistically significant improvement in both end-points.

4. The panel concluded that the PMA is approvable, based on the effectiveness data presented above. However, because the proposed indications for use included use with any chemotherapy agent and because FUDR was the only agent used during clinical trials, the panel recommended a post-approval study, which was to have collected data on results with other chemotherapy agents and may have contributed to a better understanding of survival. The panel stated that an observational study would suffice. CDRH considered the need for a post-approval study and concluded that a study to bolster the survival data would have to be a randomized, controlled trial similar to the pre-market study, but larger. However, given that the indications for use have been limited to use with FUDR only and given that survival is not a necessary end-point and that tumor regression and increased time to progression are more appropriate end-points, CDRH concluded that there is no need for a mandatory post-approval study.

Therefore, CDRH concluded that SIR-Spheres® is effective in tumor regression and increased time to tumor progression and that there is no need for a post-approval study.

The Panel also recommended a modification to the sponsor's proposed patient labeling. CDRH does not believe that patient labeling is mandatory for this device. Our reasons for this determination are: 1) Sir-Spheres® is for professional use only; 2) Prior to use, the patient will receive counseling on the use, potential benefits, and potential complications of the device from the attending physician; and 3) There are numerous sources (American Brachytherapy Society, American College of Radiology, etc.) of patient information and counseling on these types of radiation therapy products that can provide information to the patient.

CDRH recommended approval of the device for marketing. The applicant's manufacturing facility was inspected on October 10 and 14, 2001 and was found to be in compliance with the Quality Systems regulations. FDA issued an approval order on March 5, 2002.

XV. Approval Specifications

Directions for use: See the attached labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, and Precautions in the attached labeling.

Postapproval Requirements and Restrictions: See approval order.