U.S. Nuclear Regulatory Commission (NRC)

Advisory Committee on the Medical Use of Isotopes (ACMUI)

Subcommittee on Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and Sir-Spheres® Licensing Guidance, Revision 10

Final Report

Submitted on: May 9, 2019

Subcommittee Charge

The Subcommittee's charge was to review the staff's draft Revision 10 of the *Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and Sir-Spheres® Licensing Guidance* and provide any comments or recommendations for change/acceptance of the guidance.

Subcommittee Members

Dr. Vasken Dilsizan
Ms. Melissa Martin
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Introduction

Yttrium-90, a pure beta emitter, decays to stable zirconium-90 with a physical half-life of 64.1 hours (2.67 days). The average energy of the beta emissions from yttrium-90 is 0.9367 MeV with an average penetration range of 2.5 mm and a maximum range of 11 mm in tissue. Following delivery of the yttrium-90 microspheres in tumorous liver tissue, the microspheres provide an embolic effect and the beta radiation emitted provides a therapeutic effect. The microspheres are delivered into the liver tumor through a catheter placed into the hepatic artery that supplies blood to the tumor. The microspheres, 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. There are currently two Y-90 based microsphere devices that have been reviewed by the FDA. They differ slightly in composition of the spheres and in the patient population for which they are approved.

TheraSphere® consists of insoluble glass microspheres where yttrium-90 is an integral constituent of the glass. A preassembled single use TheraSphere® Administration Set is provided for each dose. Also provided are re-usable accessories including an acrylic box base, top shield, removable side shield, bag hook and a RADOS RAD-60R radiation dosimeter (or equivalent). TheraSphere® is an approved HDE device indicated for use in radiation treatment

or as neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters.

SIR-Spheres® microspheres consist of biocompatible resin microspheres containing yttrium-90 with a size between 20 and 60 microns in diameter. The administration set includes a delivery box (an acrylic box base), delivery set (including all the catheters and connectors), and a V-vial (including the shielding). Sir-sphere are an approved PMA device for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intrahepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

Background

The "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and Sir-Spheres® Licensing Guidance" was published in 2002 and revised in 2004, 2007, 2008, 2011 and 2016. NRC staff, stakeholders and the ACMUI identified numerous issues that needed to be addressed. NRC staff and Agreement State Representatives formed a working group to address the issues and make any necessary revisions. Revision 10 updated the criteria for training and medical event reporting, inventory requirement specifications, and waste disposal issues and aligned the guidance with the Part 35 rule entitled "Medical Use of Byproduct Materials—Medical Event Definitions, Training and Experience, and Clarifying Amendments" which went into effect on January 14, 2019 for NRC licensees.

Overall, the Subcommittee believes this is a well written and documented licensing guidance document. The Subcommittee endorses the draft Revision 10 of the licensing guidance, subject to the specific changes outlined below.

Specific Changes to the Guidance Considered by the Subcommittee and its Recommendations

Page 8, section iii, line 3: The current section reads…*to support training provided by a Y-90 microsphere manufacturer representative involving*: We suggest defining what manufacturer's representative means. This will help to ensure the manufacturer's trainer has the proper experience.

Page 9, section B, paragraph 2, line 2: This section currently reads… *unsupervised use should include at least 3 hands-on patient cases for each type of Y-90 microsphere requested.* We suggest keeping three hands on cases for each type of microsphere delivery device. The Y-90 spheres are slightly different (glass or polymeric) and the delivery systems of the two devices have different characteristics. This will ensure that the user has documented experience with both device types.

Page 11, section 4.2, line 4: The current sentence reads, "…*An RSO already listed on a license that includes one type of microsphere device does not require additional approval for the other type of microsphere device*…" We suggest adding to the end of the sentence, *"but should be familiar with all devices used at the facility."*

Page 13, section 5.1, paragraph 1, last sentence: The current sentence reads, "… *Unexpected dose or activity to an organ or tissue other than the treatment site that is caused by catheter placement during delivery of the y-90 microspheres is not considered shunting."* We suggest adding *"and should be evaluated as a possible medical event"* to the end of the sentence.

Page 14, section 5.2, paragraph 3, line 2: The current sentence reads, "…*the treatment site, the radionuclide (including the physical form (Y-90 microspheres)); the model of spheres e.g. TheraSpheres® or Sir-Spheres®) or manufacturer, the prescribed dose or activity, and if appropriate for the type of microsphere used, the statement 'or dose or activity delivered at stasis"*. We suggest describing the site to be treated more specifically (left lobe, right lobe)

Page 14, section 5.2, paragraph 3, line 4: The current sentence reads, *"…the treatment site, the radionuclide (including the physical form (Y-90 microspheres)); the model of spheres e.g. TheraSpheres® or Sir-Spheres®) or manufacturer, the prescribed dose or activity, and if appropriate for the type of microsphere used, the statement 'or dose or activity delivered at stasis"*. We suggest adding activity, date of administration and route of administration

Page 14, section 5.2, paragraph 4, line 6: The sentence currently reads, *"…anatomical description of the tissue intended to receive a radiation dose…"* We suggest changing *tissue* to *tissue(s).* Segmented doses may be delivered to various anatomic locations.

Page 15, section 5.3, paragraph 1, line 3: The current sentence reads, *"…as a result from patient intervention, as defined in 10 CFR 35.2..."* We question if the term "intervention" should be defined in the guidance document.

Page 16, section 5.3, paragraph 1, line 1: The sentence currently reads "…*organ or tissue other than the treatment site…"* We suggest that treatment site should be *intended treatment*.

Page 16, section 5.6, paragraph 2, line 2: The current sentence reads *"label syringes and syringe radiation shields with the radioactive drug."* We believe the label should be explicit and include patient name, device type, dose and date, and treatment site, if feasible. The term radioactive drug should be changed to device type since these products are licensed as medical devices and not drugs.

Other Recommendations

There are no other recommendations from the subcommittee.

The ACMUI unanimously approved this report, during its spring 2019 meeting on April 3, 2019.

Respectfully Submitted on May 9, 2019,

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