Nuclear Regulatory Commission (NRC)

Advisory Committee on the Medical Uses of Isotopes (ACMUI)

Sub-Committee on

Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSpheres

and SIR-Spheres Licensing Guidance

Draft Report

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Introduction

The liver is a common site for primary and secondary malignancies. The traditional management of these diseases has been either surgical and/or by chemotherapy, the latter by oral, intravenous or intra-arterial. Over the last several years, the introduction of transarterial radioembolization with yttrium-90 (Y-90) impregnated microspheres has emerged as an important therapy in the management of hepatic malignancies[1].

Y-90 microspheres are manual permanent brachytherapy implants which are small, with a diameter of 20-60 microns for resin microspheres and 20-30 microns for the glass microspheres. These radiolabeled microspheres are delivered intra-arterially, usually by an interventional radiologist. Y-90 microspheres are regulated under 10 CFR 35.1000 “Other Medical uses of Byproduct material or Radiation from Byproduct material.”

[1] Kallini JR, Gabr A, Salem R, et al. Transarterial Radioembolization with Yttrium-90 for the Treatment of Hepatocellular Carcinoma. Adv Ther. 2016;33:699-714

Background

The draft Revision 10 of the NRC licensing guidance on Y-90 Microsphere Brachytherapy Sources and Devices is near complete. This ACMUI subcommittee was tasked to provide comments on the following:

1) the removal of the authorized user (AU) manufacturer training Pathway 2;
2) update of the waste and disposal section on long-lived impurities; and
3) addition of a section on autopsy and cremation of Y-90 microsphere patients.

The removal of AU Pathway 2

The draft NRC "Yttrium-90 Microsphere Brachytherapy Sources and Devices: TheraSpheres and SIR-Spheres Licensing Guidance, Revision 10" outlines the updated qualifications of an AU for Y-90 microspheres as well as the required training and experience. The required clinical experience of 3 supervised hands-on patient cases continues to be allowed through either of two pathways.

Pathway 1: A physician seeking AU status for Y-90 microsphere therapy has work experience with the specific microsphere therapy for which approval is being sought by performing 3 hands-on supervised cases under the direct supervision of one or more qualified physician AUs for that specific Y-90 microsphere therapy; or

Pathway 2: A Y-90 microsphere manufacturer supervises 3 in-vitro simulated Y-90 microsphere cases for the type of therapy for which approval is being sought, after which the individual is listed on the institutional license and commits to completing the first 3 patients as hands-on supervised cases under the direct supervision of the manufacturer's representative within 6 months of being listed on the license.

However, the draft guidance document proposed the elimination of Pathway 2, which was established in 2004, with a 2-year deadline date. AU candidates will be able to initiate Pathway 2 up to the deadline date. The NRC/OAS Working Group provided the following rationale for eliminating Pathway 2:

1. After more than a decade of AU and manufacturer training, the current number of AUs is sufficient to meet the clinical demand and provide the required clinical use experience for training new AUs.
2. Tracking the AUs listed on a license who have or have not completed the required 3 hands-on manufacturer-supervised therapies is difficult and at times impossible. Consequently, there potentially could be individuals listed as AUs who have not completed the required supervised clinical cases before performing these therapies on their own.
3. The use of non-physician proctors providing clinical experience for radionuclide therapy by physicians is less than optimal.

The proposed elimination of Pathway 2 raises concern whether there are sufficient training and experience opportunities for new AUs, especially in those cases where the therapy use is new for a medical licensee. The subcommittee considered whether the Pathway 2 elimination could have a negative effect on patient safety or cause potential delay or limited access for patient care, particularly in rural communities. The subcommittee also considered that manufacturer training provides a uniform standard of didactic and in-vitro clinical training which may not be provided by physician AUs who may also be unable to supervise cases due to time constraints (i.e., "too busy') or co-operation issues between institutions or networks.

With the elimination of Pathway 2, it is the subcommittee's opinion that if there is a sufficient need for Y-90 AU microsphere training, institutions that perform large numbers of these treatments will likely offer "mini fellowships" to satisfy training or experience needs, and could be done in coordination with the manufacturer's didactic and in-vitro clinical training program. Furthermore, an AU approved for a specific type of Y-90 microsphere therapy can be named as an AU at another institution which performs or will perform that Y-90 microsphere therapy without need to do additional training or experience. The subcommittee also encourages current AUs for Y-90 microsphere therapy to support the proctoring experience for AU Y-90 microsphere therapy within their communities.

The subcommittee did not reach a consensus in the phase out of the Pathway 2 option following their review of the subcommittee's considerations and suggestions on addressing training and experience needs after elimination of the Pathway 2 option.

Y-90 waste and disposal

Y-90 microspheres can be generator- or reactor- produced, resulting in a range of impurities with widely varied half-lives. According to 10 CFR 35.92, byproduct material with a physical half-life of 120 days or less (short-lived) may be held for decay-in-storage before disposal. Y-90 microspheres contain both short-lived (Y-88 and Y-91) and long-lived impurities (i.e., europium-152, europium-154, cobalt-60, strontium-90) from reactor production. Licensees need to be aware of these long-lived impurities as they may present disposal issues. Y-90 vials, in which no measurable impurity activity is detected, may be held for decay- in-storage. Y-90 vials with measurable long-lived impurity activity, however, need to be returned to an authorized manufacturer or transferred to an authorized recipient.

The section of the Rev. 10 draft license guidance entitled "Waste Disposal Issues" was updated to provide additional information on the potential longer-lived contaminants that may be found in Y-90 microspheres, and continues to refer the reader to NRC Information Notice 2007-10, along with updated journal references for additional information. Specifically, the draft guidance states, "Although impurities need not be listed on an NRC license; licensees are responsible to ensure the microspheres are handled and disposed of in accordance with 10 CFR Part 20 and Part 35 requirements." The reader is provided the same routes of disposal to consider as have been listed since the September 2007 (Rev. 3) update. In addition, the reader is referred to Regulatory Information Summary 2004-17, Revision 1 for more information regarding requirements for holding waste for decay-in-storage.

The subcommittee supports inclusion of this additional guidance information on Y-90 waste and disposal in the NRC Rev. 10 draft guidance. One minor suggestion is to remove the two uses of the word, "recently," in the first paragraph of this section. Use of that word would eventually need to be changed in subsequent updates, and is not necessary for this update.

Autopsy and cremation

A section of the Rev. 10 draft license guidance entitled "Autopsy and Cremation" is added to note that handling the body of a deceased Y-90 microspheres patient may require additional radiation precautions. A healthcare worker's radiation exposure can be increased by handling Y-90 microsphere impregnated autopsy tissue. Y-90 microsphere therapy involves millions of permanent brachytherapy particles that are not biodegradable. As a pure beta emitter, Y-90 has a physical half-life of 64 hours and a tissue range of 11 mm. The draft guidance refers the

reader to NCRP Report No. 155 and to NUREG-1556, Volume 9, Appendix N for additional information and guidance.

The subcommittee supports inclusion of this section on autopsy and cremation in the NRC Rev. 10 draft guidance. One suggestion is to include a description as to the timing of the autopsy as it relates to the Y-90 microsphere therapy and why additional radiation precautions may need to be considered. The subcommittee recommends the following edit:

> "Patients treated with Y-90 microspheres will not usually present an external radiation hazard to persons handling the deceased's body. However, if the autopsy is performed within two to four weeks after the Y-90 microsphere therapy, an autopsy healthcare worker's radiation exposure may increase due to the handling of Y-90 impregnated tissue, which could still contain a significant number of the high energy, beta-emitting Y-90 microspheres. Cremation occurring within this same timeframe may also necessitate additional precautions due to the remaining Y-90 microspheres, and potentially beyond four weeks due to long-lived contaminants[2]."

Respectfully submitted, September 13, 2016.

Sub-Committee on Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSpheres and SIR-Spheres Licensing Guidance, Revision 10
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[2] Nelson K, Vause PE, Koropova P. Post-mortem considerations of Yttrium-90 90Y microsphere therapy procedures. Health Phys. 2008 Nov; 95(5 Suppl):S156-61.