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Chairman Kristine L. Svinicki
Commissioner Jeff Baran
Commissioner Annie Caputo
Commissioner David A. Wright
U.S. Nuclear Regulatory Commission
11555 Rockville Pike
Rockville, MD 20852

Re: SECY-20-0005, Rulemaking Plan for Training and Experience Requirements for Unsealed Byproduct Material (10 CFR Part 35)

Dear Commissioners:

The purpose of this letter is to urge you to choose Option 1: Status Quo instead of the staff-recommended Option 3. I have reviewed this document carefully and note errors and omissions that are significant. I also note the NRC staff who ignored the comments of the Society of Nuclear Medicine and Medical Imaging (SNMMI), the American College of Nuclear Medicine (ACNM), the American Board of Nuclear Medicine (ABNM), the American Society of Therapeutic Radiation Oncology (ASTRO), the American College of Radiology (ACR), the American Medical Association (AMA), and the Advisory Committee on Medical Uses of Isotopes (ACMUI) and do not even discuss the points raised by these groups. NRC's "public comment" effort is completely misleading as the staff is permitted to ignore all comments that don't suit them. All these groups support Option 1.

In addition to keeping Option 1 I would add inspection of residency programs in Diagnostic Radiology and Radiation Oncology to ensure compliance with 35.390 and the Memo of Understanding between the American Board of Radiology (ABR) and the NRC. Over the past 18 years of 35.390 no inspection has ever occurred, and these programs are generally not in compliance. By getting rid of hourly requirements as stated in Option 3, the staff conveniently can ignore the nation-wide noncompliance issue. **There is too much money at stake from licensing fees, and the real reason for this whole rulemaking is to bring in more licensing fees to support Medical Program staff.**

A letter to the NRC from Spectrum, maker of Y-90 Zevalin, and Bayer, maker of Ra-223 dichloride (Xofigo) charged that there are not enough Authorized User (AU) physicians

in the U.S. to perform therapies, and they wanted a mechanism to make other physicians AUs with decreased training requirements. In the SECY paper, NRC staff and management only included Nuclear Medicine physicians and Radiation Oncologists as AUs at present, and left out the Diagnostic Radiologists, who are also AUs. **There is no shortage of AUs.** The problem with Y-90 Zevalin is that it is not a very good drug. Zevalin is a mouse monoclonal antibody to CD-20 receptors found on most B cell lymphomas. A humanized form of the antibody is called Rituxin, a non-radioactive drug for treating B-cell lymphoma. While Y-90 Zevalin appeared to be superior to Rituxin in head-to head trials, the time to progression was the same and life span was the same, so there was no real advantage to Y-90 Zevalin long term. In addition, numerous non-radioactive drugs have been developed in recent years to treat B cell lymphoma that are better than Y-90 Zevalin. Hematologists-oncologists therefore have little use for Y-90 Zevalin. Take UCLA, for example. We have a very active Hematology-Oncology group and a Nuclear Medicine division with six board-certified Nuclear Medicine physicians with backgrounds in Internal Medicine and a full-time fellow board-certified in Nuclear Medicine. Nuclear Medicine at UCLA prides itself on being very active in therapy, and even participates in clinical trials for new therapy radiopharmaceuticals. **UCLA Nuclear Medicine physicians have not been asked to perform a Y-90 Zevalin therapy in about 15 years.** As to Xofigo, this is a "me too" radiopharmaceutical with two other radiopharmaceuticals approved for treating bone metastases, Sr-89 dichloride (Metastron) and the more popular Sm-153 EDTMP (Quadramet). Both are beta emitters. A Quadramet administration is one injection only and costs about $6000. Xofigo is an alpha emitter, and an administration is six injections, each given four weeks apart. It costs about $67,000 for the six injections. While alpha emitters are a good idea if the radiopharmaceutical gets into a cancer, this is not the case for any of these three radiopharmaceuticals. They get to bone mineral being laid down by osteoblasts trying to counter the damage done by the bone metastases. So, the metastases are irradiated from their outside edge, not from within. Because alphas travel very short distances in tissue, the idea is to "shave off" a bit of metastatic tissue with each injection. Patients appear to have some pain relief after the first couple of Xofigo administrations, but not after the rest, possibly because the osteoblasts have been killed by the alphas, do not make bone mineral, and the Xofigo is not taken up. There is little repair of alpha radiation damage because the damage is so dense, which is why alphas have a Relative Biological Effectiveness (RBE) of 10-20 relative to low Linear Energy Transfer (LET) x-rays, gamma rays, and beta particles. Repair of the low LET beta radiation damage keeps the osteoblasts alive and functioning. **A head-to-head trial of Xofigo vs. Quadramet has not been done, but Quadramet might well win.** In addition, Xofigo was approved only for patients with prostate cancer metastases and no other known metastases and that the bone metastases do not respond to castration. Metastron and Quadramet were approved for bone metastases from any cancer with no other constraints.

Another important aspect of radiopharmaceutical therapy is that nearly all of it requires diagnostic imaging studies beforehand. So, patients will already be at a facility doing diagnostic imaging, and they might as well stay there to get their therapy. This is called "theranostics". Therapy is not done in a void. Some of this imaging is sophisticated, requiring positron emission tomography (PET) drugs and PET-computed

tomography (CT) cameras. Some require single photon emission computed tomography (SPECT)/CT cameras and availability of diagnostic drugs made on site or close by. This is not going to be available in small rural towns and villages, and so patients will be traveling to cities anyway. In addition, specialists such as hematologist-oncologists and urologists will not be in small rural towns and villages, but in institutions in which full service Nuclear Medicine, Diagnostic Radiology, and Radiation Oncology are available. There is no need for hematologist-oncologists and urologists to become AUs.

In addition, this SECY paper states on p.3 Enclosure 1 that Hematologist/Oncologists "...are customarily trained in radiation precautions." This is untrue. They are not, but the NRC staff may well not appreciate what adequate training involves. The purposely inaccurate statements and mathematics in NRC's Appendix U for administration of therapy radiopharmaceuticals shows that the NRC staff and management do not have the necessary competence in external dosimetry. While we have tried to fix this NRC misleading information for nearly 23 years, no repairs have been made and the staff is making plans to increase the required information and documentation, **grossly interfering with medical practice**. The NRC staff opines that the current T&E requirements interfere with the practice of medicine. They don't really---they just ensure safety and competence. Appendix U, however, definitely interferes with medical practice. **The NRC staff and management do not have expertise in quantitation of internal dose and patient-specific dosimetry, which is the coming effort in radiopharmaceutical therapy.** The NRC staff and management clearly does not understand modern radiobiology, which is critical knowledge for radiopharmaceutical therapy. Hematologist/Oncologists learn virtually nothing about these subjects.

On p.2 of Enclosure 3 it states, "Radiopharmaceutical therapies are expected to increase from 13 percent of the global nuclear medicine market in 2017 to 60 percent of the market by 2030." As far as the American market is concerned, we do many more diagnostic tests so our percent of therapy procedures is much lower. At UCLA, for example, which has a high number of therapy procedures, only 4 percent of total procedures are therapeutic. The thought that procedures will increase to 60% by 2030 in the U.S. seems incredibly far-fetched, and with our current FDA is basically impossible. The old Atomic Energy Commission approved three therapy radiopharmaceuticals, I-131 NaI for thyroid diagnosis and therapy, P-32 sodium phosphate for polycythemia rubra vera, and P-32 chromic phosphate for intracavitary treatment to stop fluid formation. Neither P-32 radiopharmaceutical has much use today. These drugs were grandfathered by the FDA, which took over radiopharmaceuticals in 1975. From 1975 through 1999 FDA approved Metastron and Quadramet for treatment of bone metastases. From 2000 to the present FDA approved Zevalin, Bexxar (another radiolabeled antibody against CD-20 receptors labelled with I-131), Y-90 resin microspheres (Sir Spheres) for liver tumors, Xofigo, Lu-177 dotatate (Lutathera) for neuroendocrine tumors, and I-131 MIBG (Azedra) for pheochromocytoma and paraganglioma. Bexxar was more difficult to use than Zevalin, especially with NRC's guidance, and went off the market after several years. Sir Spheres are used occasionally, and Xofigo is used occasionally. Lutathera and Azedra are approved as orphan drugs for rare diseases. This category of drugs has an easier approval process than other drugs, and these radiopharmaceuticals are not used too

often. The FDA isn't exactly tripping over its feet to approve therapy radiopharmaceuticals. Lu-177 prostate specific membrane antigen (PSMA) is still experimental here, while it has been used for years in the European Union. FDA has not yet approved Ga-68 PSMA for diagnostic purposes, but some patients receive it because of clinical trials. If your patient shows active uptake, if he's lucky, he can be part of the clinical trial of Lu-177 PSMA. Otherwise, he can either go to the EU for treatment or go without. Maybe in another year it will be approved here. Or maybe longer. Then FDA will approve it for the narrowest possible indication in order to squeeze manufacturers to submit data for other indications and maximize the yearly FDA User Fees. CMS will limit its reimbursement for only the approved indication, and private insurers will follow in lock step. Usage may not be as great as envisioned. Of course, new diagnostic radiopharmaceuticals are occasionally being approved as well, so I see no significant increase in the percentage of therapy radiopharmaceuticals in the U.S. by 2030. The NRC staff alludes numerous times to many new therapy radiopharmaceuticals with increasing complexity, but I don't see that we will have that many new therapies. I don't know what that ominous "increasing complexity" means, but for Lutathera an amino acid solution must be infused with Lutathera to protect the kidneys, but this is not complex. **There is a move towards personal dosimetry using quantitative diagnostic imaging, and this may improve the therapy drug performance. This is complex, but well-trained Nuclear Medicine physicians will have no trouble with this. For those physicians with minimal and insufficient training and experience it will likely prove too difficult to perform.**

Please realize that in every other first world country, and many third world countries, only physicians board-certified in Nuclear Medicine may practice any or all of Nuclear Medicine. **The United States is the only country chopping up the specialty into little bits to optimize licensing fees.** This degrades the specialty, promotes poor quality studies, and does a disservice to American patients. The staff equates medical quality with reported medical events, but this is absolutely untrue. Medical event reporting only measures human error. This can be reduced but never wiped out and means little. Did the patient get the best possible study, performed in a manner that optimizes the chances of a helpful answer to the primary clinician's question, or did a technologist simply perform the requested study, using a "one size fits all" approach, supply a tentative report to the radiologist, who signs it and bills? In many radiologist practices, the technologist is not supervised by the radiologist. The radiologist is supervised by the technologist. This is unfortunate for the patient, and this is what the Agreement States want to change. The way to do it is to require that the radiologist have substantial training and experience in both diagnostic and therapeutic Nuclear Medicine, as required in Part 35, so that technologists are truly supervised by competent physicians.

I urge you to choose Option 1.

Thank you for your attention and consideration.

Sincerely,

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