SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

[Submitted electronically via www.regulations.gov]

November 6, 2017

Ms. Annette Vietti-Cook
Secretary, U.S. Nuclear Regulatory Commission (NRC)
11555 Rockville Pike
Rockville, MD 20852
Washington, DC 20555-0001

ATTN: Rulemakings and Adjudication Staff

Re: Docket No. PRM–30–66; NRC–2017–0159, Naturally Occurring and Accelerator-Produced Radioactive Materials; Petition for Rulemaking; Notice of Docketing and Request for Comment

Dear Ms. Vietti-Cook:

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) appreciates the opportunity to comment on the petition for rulemaking on behalf of the Organization of Agreement States (OAS) (the Petitioner) dated April 14, 2017, requesting that the NRC revise its regulations to add radionuclides and their corresponding activities to the list of "Quantities of Licensed Material Requiring Labeling," in the Federal Register Vol. 82, No. 162, Pages 39971-72.

The Society of Nuclear Medicine and Molecular Imaging's more than 17,000 members set the standard for molecular imaging and nuclear medicine practice by creating guidelines, sharing information through journals and meetings, and leading advocacy on key issues that affect molecular imaging and therapy research and practice.

SNMMI agrees with the Organization of Agreement States petition for rulemaking. This petition is well supported by the findings of the Advisory Committee on the Medical Use of Isotopes (ACMUI) Germanium-68 (Ge-68) Decommissioning Funding Plan (DFP) Final Report of August 12, 2015 (ACMUI Ge-68 report). A copy may be found on the NRC website.
(ACMUI Ge-68 report).[1]

Question 1. What products or technologies, other than the germanium-68 generators cited in the petition, are being or could be negatively affected because the radioactive materials required for these products or technologies are not currently on the table in appendix B of 10 CFR part 30?

[1] A copy may be found on the NRC website at: https://www.nrc.gov/docs/ML1523/ML15231A047.pdf

Table 1 (below) lists radionuclides currently under development and research with half-lives greater than 120 days that are not listed in Part 30 App B.

Three radionuclides (Ac-227, Th-228 and Ti-44) are for potential radionuclide generators. Silicon-32 is a beta emitter with potential therapeutic applications. Sodium-22 and Al-26 are positron emitters with potential diagnostic applications. Two radionuclides (Ac-227 and Lu-177m) are potential radionuclidic contaminants in radiopharmaceuticals.

Table 1.Radionuclides currently under development or being investigated for possible use as radiopharmaceuticals

Radionuclide	Decay Mode	Half-Life	Part 30 App B Quantity (µCi)	DFP trigger (µCi) (App B value times 10^5)
Ac-227[1]	α	21.772 y	0.01*	1,000
Th-228[2]	α	1.9125 y	0.01*	1,000
Si-32	β^-	153 y	0.1*	10,000
Ti-44[3]	ε	59.1 y	0.1*	10,000
Na-22	β+	2.6018 y	0.1*	10,000
Al-26	β+	7.17e5 y	0.1*	10,000
Lu-177m[4]	IT	160.44 d	0.1*	10,000

1. Radiocontaminant in Ac-225 or as a potential generator; parent for Th-227 ($t_{1/2}$ = 18.7 d) and Ra-223 ($t_{1/2}$ = 11.4 d).
2. Potential generator; parent for Ra-224 ($t_{1/2}$ = 3.6d) and Pb-212 ($t_{1/2}$ = 10.6 h) and Bi-212 ($t_{1/2}$ = 1 h)
3. Potential generator; parent for Sc-44 ($t_{1/2}$ = 3.9 h)
4. Radiocontaminant in Lu-177

Question 2. Please provide specific examples of how the current NRC regulatory framework for decommissioning financial assurance has put an undue hardship on potential license applications. Explain how this hardship has discouraged the development of beneficial new products or otherwise imposed unnecessarily burdensome requirements on licensees or members of the public (e.g., users of medical diagnostic or therapeutic technologies) that depend on naturally occurring or accelerator-produced radioactive materials (NARM).

The framework for decommissioning financial assurance cannot be considered without first mentioning the hardships that the decommissioning funding plan (DFP) imposes on medical license applicants. The preparation of a DFP is a very complex and time-consuming effort that is unique, applicable only to a single license. The complexity of the process can be seen from the 28-page NRC DFP Template v1.[2] Furthermore, a DFP cannot be used by the same licensee at another location. This burden is a particular

[2] *See* http://www.doh.wa.gov/Portals/1/Documents/4100/decmtemp_m.doc

hardship for a medical licensee who has several locations of use in their radioactive materials license. Under current regulations, all of these locations of use must be considered in the preparation of their DFP even if the radionuclide in question is only used at one of the locations. Examples of these hardships and burdens are described in detail in the Ge-68 ACMUI report. It is reasonable to expect that the same hardships and burdens experienced by Ge-68 generator users would also be experienced by users of the radionuclides identified in Table 1. It is clear that an increasingly regulatory burden will be incurred as in the recent scenario with the Ge-68 generator. Limitations and delays in patient care have occurred and will continue to occur because of the expensive financial assurances process that has to be addressed under the current DFP trigger amounts of 1 to 10 mCi.

It is also evident that DFP requirements and FA amounts were originally developed primarily for single site nuclear facilities. The scope of work required when this is extended to a commercial radiopharmacy network; for example, one with numerous pharmacies in numerous states, is astronomical. This is the task currently at hand for more than one radiopharmacy network that is trying use Ge-68/Ga-68 generators to provide patients access to Ga-68 radiopharmaceuticals in a similar fashion to the way Mo-99/Tc-99m generators provides patients access to Tc-99m radiopharmaceuticals.

A specific example of a hardship to a licensee happened with Lu-177m, which is not currently listed in appendix B of 10 CFR part 30. Lu-177m is a radionuclidic contaminant in the radiopharmaceutical Lu-177-labeled DOTATATE. Ebrahim Delpassand, Board Certified Nuclear Medicine physician, Chairman and Medical Director at Excel Diagnostics and Nuclear Oncology Center and former deputy Chair at the University of Texas MD Anderson Cancer Center, ran into activity possession limitations due to the restrictive limits for Lu-177m. As a result, they often had patients seeking treatment with Lu-177-labeled DOTATATE, but they were unable to purchase the needed quantities Lu-177 due to the NRC limits. This example demonstrates the inequity of applying 10 CFR 30.35 in different states. Lu-177 DOTATATE was approved as an investigational new drug (IND) by the Food and Drug Administration (FDA) with the knowledge of the presence of the Lu-177m contaminate and deemed safe to administer to patients under the Excel's FDA approved IND application. Many licensees have not had this issue with the same radiopharmaceutical radionuclidic contaminate from their respective state regulatory agencies. In these other situations, the states used appropriate regulatory discretion and did not require a DFP and financial assistance (FA).

Question 3. Given NRC's current regulatory authority over the radiological safety and security of NARM, what factors should the NRC take into account in establishing possession limits for any of these materials that should be listed in appendix B of 10 CFR part 30?

The NRC should consider the unique nature of the radionuclides used in radiopharmaceuticals, which are administered to patients for a diagnostic or therapeutic benefit. The NRC should also consider that these radiopharmaceuticals have already undergone extensive evaluation before they are approved for use in humans by the FDA. Radiopharmaceuticals are unique and deserve special consideration because they contain radionuclides that are intentionally administered to patients. Any rulemaking should reflect the fact that therapeutic radiopharmaceuticals are used for the advanced treatment and care of patients. Often therapeutic radiopharmaceuticals are the last treatment option available to patients with cancer, and they are being brought to market to extend these patient's lives. This use is very different from the reasons that that all other radionuclides regulated by the NRC that require a DFP or FA are used. In addition, it is our recommendation that for any radiopharmaceutical allowed under 10 CFR 35.200 or 35.300, it is not appropriate to consider radionuclidic contaminants with respect to 10 CFR 30.35 Financial Assurance and recordkeeping for decommissioning. This should be emphasized in a

guidance to promote consistent regulatory implementation across all medical licensees. The limits in appendix B for DFP requirements and FA amounts were originally developed primarily for nuclear facilities (e.g., power reactors, fuel cycle facilities, etc.), and the evolution of the medical use of radionuclides was not considered during their development. Aside from their end use, it is readily apparent that the scope and use of radioactive materials at nuclear facilities such as power reactors is very different from that found at a medical facility.[3]

Radionuclide generators should be considered as a separate category from sealed and unsealed sources of radionuclides, and should qualify for additional relief from restrictive DFP activity limits and excessive FA. The NRC can improve its DFP and/or FA amounts determination by creating a third category of radioactive material. Currently 10 CFR 30.35 has only two categories, sealed and unsealed radioactive material. A radionuclide generator cannot be classified as a sealed source, but simply because it cannot be considered a sealed source this does not mean that it is appropriate to set its DFP or FA amounts the same as those for unsealed radioactive material. The obvious solution is to update 10 CFR 30.35 by adding a new, third, category for radionuclide generators, reflecting all radioactive material and including new forms of radioactive material that the NRC now regulates.

The Ge-68/Ga-68 generator is an excellent example in that the parent radionuclide, Ge-68 is an ion absorbed onto a porous ion exchanger, it is insoluble in the eluent and stays within the generator. The generators have no moving parts and they are not susceptible to physical damage. At the end of the generator's useful life, it is returned to the manufacturer for disposal with the parent still sequestered within the generator's containment vessel. This disposal method is far and away the preferred method for a medical licensee. When the generator is returned to the manufacturer, all the Ge-68 is returned; there is no Ge-68 remaining at the medical licensee's site.

There is yet another layer of safety with these generators as the FDA is very involved in the manufacturing of these generators as components of radiopharmaceuticals. It is difficult to overstate how involved the FDA is in ensuring that these generators are safe and effective generators since their eluate is used directly (e.g., Rb-82) or indirectly (e.g., Ga-68, Tc-99m) in patients. These qualities are inherent to all radionuclide generators utilized in the production of radiopharmaceuticals and will be present in all radionuclide generators that are now under development. Since the generators are returned to the manufacturer for disposal, there is no need for a DFP for any radionuclide generator. Any required FA amount should be developed from the perspective that the "decommissioning costs" that would consist solely of the shipping and handling costs to return the generator to the manufacturer plus the costs of a close-out survey for its former location.

Regarding use of a DFP to ascertain the amount of the FA required, only the area of use of the radionuclide in question should be considered. The need to avoid a one-size-fits-all approach is recognized by the NRC, and is addressed in NRC document NRC-2015-0070. One goal in the advance notice states: "The NRC's goals in amending these regulations would be to provide an efficient decommissioning process, reduce the need for exemptions from existing regulations, and support the principles of good regulation, including openness, clarity, and reliability." We agree with this goal and believe that it would support the development of appropriate DFP and FA amounts for medical isotopes at medical licensees. As given the substantial differences between a medical licensee and a nuclear facility, clearly a one-size-fits-all approach is not consistent with the principles of good regulation. It is

[3] For example, descriptions of nuclear facilities undergoing decommissioning can be found at the NRC webpage: https://www.nrc.gov/info-finder/decommissioning/.

difficult to justify why all areas of use should be included in a DFP or FA amount since different radionuclides may be used in different areas. For example, Tc-99m would be used in nuclear medicine imaging and I-125 seeds used in radiation therapy. The areas of use for these radionuclides do not require a DFP or an FA thus including all areas of use at a medical licensee leads to unnecessary and inappropriate expenses for a DFP as described in detail in the ACMUI Ge-68 report, or as compared to the goal in the above advance notice.

Question 4. Does this petition raise other issues not addressed by the questions above about labeling or decommissioning financial assurance for radioactive materials? Must these issues be addressed by a rulemaking, or are there other regulatory solutions that NRC should consider?

The latest licensing guidance, July 13, 2017, Revision 1 and its related memorandum (link is above) are a welcome improvement.[4]

It should be noted that Ge-68/Ga-68 generators produced by manufacturers other than Eckert and Ziegler (e.g., IRE and ITG) are on the market. Both of these will have the same, if not improved, elution characteristics and should be treated in the same manner as the Eckert and Ziegler generator. In addition, larger generators are in development (up to 100 mCi), but these pose no more hazard than two 50 mCi generators. In the future, it should be clear that calculations in the guidance for determining FA amounts should focus on the total amount of Ga-68 used by a medical licensee whether this consists of two 50 mCi generators or one 100 mCi generator. New guidance should be developed to promote consistent regulatory implementation across all medical licensees for the use of these new Ga-68 generators.

SNMMI appreciates the opportunity to comment on this petition. As always, SNMMI is ready to discuss any of its comments or meet with NRC on the above issues. In this regard, please contact Caitlin Kubler, Senior Manager, Regulatory Affairs, by email at ckubler@snmmi.org or by phone at 703-326-1190.

Sincerely,

Bennett S. Greenspan, MD, M.S.

Bennett S. Greenspan, MD, FACNM, FACR
President, SNMMI

[4] Also, *See* https://scp.nrc.gov/asletters/program/sp16083_1.pdf