RulemakingComments Resource

From: Baxter, Michael <mbaxter@aphanet.org>
Sent: Friday, November 03, 2017 4:15 PM
To: RulemakingComments Resource; Vietti-Cook@nrc.gov
Cc: CHAIRMAN Resource; CMRBARAN Resource; CMRBurns Resource; Galbraith, Wendy; Mishoe, Ashley E
Subject: [External_Sender] APhA Comments 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
Attachments: APhA Nuclear SIG OAS Petition 113 Final.pdf

Greetings:

On behalf of the American Pharmacists Association-Academy of Pharmacy Practice and Management (APhA-APPM) Nuclear Pharmacy Practice Special Interest Group (SIG), please consider the following comments to the four specific questions contained in 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. (See, attached .PDF for full comment letter).

The American Pharmacists Association (APhA) was founded in 1852, and represents 64,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and other parties invested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, physician offices, ambulatory clinics, managed care organizations, hospice settings, and the uniformed services. Within APhA, the Nuclear Pharmacy Practice SIG represents over 2,200 APhA members involved in the specialty practice of nuclear pharmacy.

Thank you for this opportunity to comment. The APhA-APPM Nuclear Pharmacy Practice SIG looks forward to working with the NRC to implement the above recommendations. If you have any questions or require additional information, please contact Michael Baxter, Director of Regulatory Affairs, at mbaxter@aphanet.org or by phone at (202) 429-7538.

Sincerely,

APhA-APPM Nuclear Pharmacy Practice SIG Members

cc: Members of the APhA-APPM Nuclear Pharmacy Special Interest Group; NRC Commissioner Kristine L. Svinicki, Chairman, Commissioner Jeff Baran, Commissioner Stephen G. Burns

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[Submitted electronically via www.regulations.gov and Rulemaking.comments@nrc.gov]

November 3, 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:

On behalf of the American Pharmacists Association-Academy of Pharmacy Practice and Management (APhA-APPM) Nuclear Pharmacy Practice Special Interest Group (SIG), please consider the following comments to the four specific questions contained in 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.

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As pharmacists within the specialty practice of nuclear pharmacy, we agree with the Organization of Agreement States' (OAS) 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).[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?"

Table 1 (below) lists radionuclides currently under development and research with a half-life greater than 120 days, which are not listed in part 30 Appendix B.

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

Table 1.Radionuclides currently under development and research for medical use as radiopharmaceutical drugs

Radionuclide	Decay Mode	Half-Life	Part 30 App B Quantity (µCi)	DFP trigger (µCi) (App B value times 10^5)
Ac-227[1]	α	21.772y	0.01*	1,000
Th-228[2]	α	1.9125y	0.01*	1,000
Si-32	β^-	153y	0.1*	10,000
Ti-44[3]	ε	59.1y	0.1*	10,000
Na-22	β+	2.6018y	0.1*	10,000
Al-26	β+	7.17e5y	0.1*	10,000
Lu-177m[4]	IT	160.44d	0.1*	10,000

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

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

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 hardships that the decommissioning funding plan (DFP) has on medical license applicants. The preparation of a DFP is a very complex and time-consuming effort that is unique and applicable to a single license. The complexity of the process can be considered in the 28-page NRC DFP Template v1.[2] A DFP cannot be used by another licensee location. This burden is particularly a hardship for a medical licensee who has numerous 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 location of the licensee. Examples of these hardships and burdens are described in detail in the Ge-68 ACMUI report. It is very reasonable to expect that the very same hardships and burdens experienced by the Ge-68 generator user would also be experienced by users of the radionuclides identified in Table 1. It is clear that an increased regulatory burden will be incurred as in the recent scenario with the Ge-68 generator. Limitations and delays in patient care have 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 financial assurance (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 on 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, M.D., a 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 listed for Lu-177.[3] The result was they often had patients seeking treatment but were unable to receive the needed

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

[3] Oral communication to Cathy Cutler, Ph.D., Director of Medical Isotope Research Production and Development program (MIRP) at Brookhaven National Laboratory from Ebrahim Delpassand, M.D., a physician at Excel Diagnostics, at the SNMMI/CORAR; OAS proposed NRC rule making stakeholder teleconference on October 18, 2017.

quantities of activity due to the restrictive NRC limits. This example in Texas 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 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 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 intentionally 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 as they are intentionally administered radionuclides to patients. Any rule making should reflect radiopharmaceuticals as advanced treatment and care for patients. Often radiopharmaceutical therapies are the last option for patients in their course of cancer treatment and are being brought to market to improve and extend their patient life. This use represents one that is essentially antithetical to purpose of use for all other radionuclides regulated by the NRC requiring a DFP or FA. 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 the radionuclidic contaminant 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. 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.) which never considered the evolution of medical use and the implications these limits would have on their development. It is readily apparent that the scope and use of radioactive material at these nuclear facilities are far different from those found at a medical license.[4]

Radionuclide generators should be considered as a separate category, besides sealed and unsealed sources of radionuclides, and qualify for additional relief from restrictive DFP activity limits and excessive FA. The NRC can improve its DFP and/or FA amounts determination with a third category of radioactive material (i.e., radionuclide generator). Current 10 CFR 30.35 has two categories, sealed and unsealed radioactive material. A radionuclide generator can nearly be classified as a sealed source, because its long-live parent radionuclide is designed to remain in the generator. It is also not appropriate to set the DFP or FA amounts for radionuclide generators the same as those for unsealed radioactive material. 10 CFR 30.35 needs to be updated to appropriately reflect all radioactive material, including a new form of radionuclide generator that the NRC regulates.

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

The Ge-68/Ga-68 generator is an excellent example in that the parent radionuclide, Ge-68 stays within the generator. The generators have no moving parts, once placed in a lab it is not moved, it's 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 sequestered inside of the generators containment vessel. This disposal method is by far and away the preferred method by 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. There is yet another layer of safety with these generators as the FDA is very involved in the manufacturing of these generators as components in radiopharmaceutical drugs. It is difficult to overstate how involved FDA is in the agency's efforts to ensure that safe and effective generators are produced by manufacturers since their eluate is used directly or indirectly with patients. These same safe qualities are inherent to all radionuclide generators utilized in drugs for medical use and will be present in future radionuclide generators 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 realistic perspective of radionuclide generator decommissioning that would consist of the shipping and handling costs to return the generator plus the costs of a close out survey for its former location.

Regarding a DFP as used to ascertain the amount of FA required, only the area of use of the radionuclide in question should be considered. The need to avoid a one-size-fits-all is recognized by the NRC, as is addressed in the NRC document NRC-2015-0070.[5] One goal in the advance notice is: "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 does not fit with the principles of good regulation. It is difficult to justify why all areas of use should be included in a DFP or FA amount. For a medical licensee, different radionuclides are used in different areas, e.g., Tc-99m in nuclear medicine imaging and I-125 seeds in radiation therapy. These areas of use on their own require no DFP or FA amount. Including all areas of use at a medical license 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 are a welcome improvement.[6]

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[5] *See* NRC. "Regulatory Improvements for Decommissioning Power Reactors." Proposed Rule. Federal Register Vol. 80, No. 223, Pages 72358-72373. November 19, 2015, available at: https://www.gpo.gov/fdsys/pkg/FR-2015-11-19/pdf/2015-29536.pdf

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

It should be noted that other Ge-68/Ga-68 generators produced by manufacturers (e.g., IRE and ITG) other than Eckert and Ziegler are on the market. Both will have the same if not safer qualities and should be treated in the same manner as the Eckert and Ziegler generator. In addition, lager generators are in development (up to 100 mCi), but 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 Ge-68 used by a medical licensee whether it is achieved with 50 mCi or 100 mCi generators. New guidance should be developed to promote consistent regulatory implementation across all medical licensees for the use of these new Ge-68 generators.

Thank you for this opportunity to comment. The APhA-APPM Nuclear Pharmacy Practice SIG looks forward to working with the NRC to implement the above recommendations. If you have any questions or require additional information, please contact Michael Baxter, Director of Regulatory Affairs, at mbaxter@aphanet.org or by phone at (202) 429-7538.

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