UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

July 13, 2017

MEMORANDUM TO: Daniel H. Dorman, Regional Administrator
Region I

Cynthia D. Pederson, Regional Administrator
Region III

Kriss Kennedy, Regional Administrator
Region IV

FROM: Marc L. Dapas, Director ***/RA/***
Office of Nuclear Material Safety
and Safeguards

SUBJECT: REVISION OF TECHNICAL BASIS FOR GRANTING SPECIFIC EXEMPTION FROM DECOMMISSIONING FUNDING PLAN REQUIREMENT FOR GERMANIUM-68/GALLIUM-68 GENERATORS

In a memorandum dated July 29, 2016 (Agencywide Documents Access and Management System (ADAMS) Accession No. ML16082A415), as the Director for the Office of Nuclear Material Safety and Safeguards (NMSS), I delegated to the Regional Administrators the authority to grant an exemption from the decommissioning funding plan (DFP) requirements in Title 10 of the *Code of Federal Regulations* (10 CFR) 30.35(a)(1). The exemption would relieve a licensee from the requirement for a DFP, for the possession and use of Germanium-68 (Ge-68)/Gallium-68 (Ga-68) generators, when certain conditions are met. Specifically, I authorized the Regional Administrators to issue an exemption, when requested, only for Ge-68/Ga-68 generators, only from the DFP requirement, and only if a legally binding agreement is in place for the licensee to return the generators to the manufacturer or distributor when the generators are no longer in use.

Enclosed is a revision to the July 29, 2016, memorandum that clarifies the technical basis for the subject exemption authorization. The revision provides (1) a clarification that granting an exemption from the DFP requirement in 10 CFR Part 30 does not exempt the licensee from other financial assurance requirements; (2) a list of specific elements that should be in a legally binding agreement for the return of generators to the manufacturer or distributor; and (3) a minor revision to the license condition that specifies that the licensee must return the Ge-68/Ga-68 generators to the manufacturer or distributor when they are no longer in use.

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Lastly, the clarification to the technical basis and guidance will not impact Ge-68/Ga-68 generators DFP exemptions that have been granted to date.

If you have any questions regarding this correspondence, please contact Said Daibes, Ph. D. at (301) 415-6863.

Enclosure:
Revision of Technical Basis for Granting
Specific Exemption from Decommissioning
Funding Plan Requirement for Germanium-68/
Gallium-68 Generators

SUBJECT: REVISION OF TECHNICAL BASIS FOR GRANTING SPECIFIC EXEMPTION FROM DECOMMISSIONING FUNDING PLAN REQUIREMENT FOR GERMANIUM-68/GALLIUM-68 GENERATORS (DATE: JULY 13, 2017)

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OFC	MSTR	MSTR	MSTR	OGC	MSTR	Tech Ed	NMSS
NAME	SDaibes	MFuller	KTapp for DBollock	EHouseman	KWilliams for DCollins	WMoore	MDapas
DATE	3/28/17	3/29/17	4/11/17	5/15/17	6/09/17	6/13/17	7/13/17

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Revision of Technical Basis for Granting Specific Exemption from Decommissioning Funding Plan Requirement for Germanium-68/Gallium-68 Generators

Germanium-68 (Ge-68)/Gallium-68 (Ga-68) generators provide access to Ga-68 labelled radiopharmaceuticals that have proven to be effective for significantly earlier diagnosis and management of neuroendocrine tumors (NET). In addition to their enhanced diagnostic capabilities and specificity, Ga-68-labelled radiopharmaceuticals also permit a reduction in effective dose compared to the currently used clinical radiopharmaceutical standard.

Because Ga-68 decays by positron emission, it is used for positron emission tomography (PET) diagnostic medical imaging procedures. Most radionuclides for PET imaging require a large and expensive particle accelerator such as a cyclotron. Compared to an accelerator, the Ge-68/Ga-68 generators have an advantage of lower cost, which permits wider availability. Having more generators available in more locations across the country is a significant advantage, because generator proximity to patients is a necessity with the 68-minute half-life of Ga-68.

Ga-68 radiopharmaceuticals developed from these generators have proven superior to the current Indium-111 (In-111) radiopharmaceutical for the early diagnosis of NETs, which include cancers of the liver and pancreas. Highly metastatic cancers in their final phases, such as NETs are difficult to diagnose, with an average of 7 years from symptom onset to confirmed diagnosis among U.S. patients. The number and variety of available treatments, including surgery and peptide receptor radionuclide therapy, make it critical to determine the extent of the disease early and accurately for proper management.

In addition to their increase in diagnostic speed and accuracy, Ga-68 labelled radiopharmaceuticals also permit reduced patient doses. The U.S. Nuclear Regulatory Commission's (NRC's) Advisory Committee on the Medical Uses of Isotopes (ACMUI) found that with Ga-68 radiopharmaceuticals, NET patients would receive nearly a five-fold reduction in effective dose compared to In-111 labelled radiopharmaceuticals. ACMUI also concluded that physicians will gain superior diagnostic accuracy, resulting in quicker diagnoses, earlier initiation of proper therapy, and improved patient outcomes.

Ge-68/Ga-68 generators operate in a manner similar to Molybdenum-99/Technetium-99m generators. They are closed systems consisting of a column containing a resin on which the parent radionuclide is fixed by adsorption. For Ge-68/Ga-68 generators, the parent radionuclide is Ge-68 which decays by electron capture to continuously produce the Ga-68 daughter product. The Ga-68 is removed from the generators by eluting it from the column with a sterile hydrochloric acid solution. The Ga-68 is soluble in the acid solution and readily elutes off the resin column.

In contrast, the parent radionuclide Ge-68 is insoluble, remains fixed on the column, and continues to decay to provide additional Ga-68 for future elutions. Some small amount of Ge-68 is present in each eluate, but as noted in the ACMUI report on Ge-68/Ga-68 generators (Agencywide Documents Access and Management System (ADAMS) Accession No. ML15231A047) and peer review references, this amount is so small it cannot be measured with a standard dose calibrator.

In accordance with Title 10 of the *Code of Federal Regulations* (10 CFR) Section 30.35, "Financial Assurance and Recordkeeping for Decommissioning," applicants must have a Decommissioning Funding Plan (DFP) to obtain a license to possess Ge-68/Ga-68 generators. Several prospective licensees have raised concerns about the resources needed to develop a DFP for these generators. After analyzing the available literature and preparing a comprehensive report on this issue, the ACMUI concluded that a DFP is not necessary to protect workers or the public from the low radiological risks associated with the use of these generators, as long as the generators are returned to the manufacturer or distributor when the generators expire and are no longer used to prepare Ga-68 for patients, or if the licensee ceases its preparation of Ga-68 radiopharmaceuticals. One reason for the decision to approve an exemption from the DFP requirement, is that the ACMUI determined that the need for decontamination due to spills or leakage from these generators would be minimal. The NRC staff independently verified ACMUI's safety basis and assumptions and agrees with the recommendations in the report.

Paragraph (a)(1) of 10 CFR 30.35 requires that:

> Each applicant for a specific license authorizing the possession and use of unsealed byproduct material of half-life greater than 120 days and in quantities exceeding 10^5 times the applicable quantities set forth in Appendix B to Part 30, shall submit a decommissioning funding plan as described in paragraph (e) of this section.

If an applicant is seeking a license to possess quantities of unsealed byproduct material less than 10^5 times the quantities set forth in Appendix B to Part 30, but greater than 10^3 times those quantities, then the applicant has the option of either submitting a decommissioning funding plan as described in paragraph 30.35(e) or a certification of financial assurance in the amount described in paragraph 30.35(d).

The amount of financial assurance required at paragraph 30.35(d) is $1.125 million for quantities greater than 10^4 but less than or equal to 10^5 times the quantities in Appendix B to Part 30, and $225 thousand for quantities greater than 10^3 but less than or equal to 10^4 times the quantities in Appendix B.

A typical new Ge-68/Ga-68 generator contains 50 mCi of Ge-68 at its calibration date. Under the NRC regulations, possession of such a generator triggers the need for a DFP. However, even if a licensee obtains an exemption from the DFP requirement, the licensee must continue to provide financial assurance. Licensees possessing more than 2 generators but less than 20 (>100 to 1000 mCi) must provide a minimum $1,125,000 in financial assurance. Licensees possessing one or two Ge-68 generators (50 to 100 mCi) must provide a $225,000 minimum in financial assurance. The basis for providing these amounts of financial assurance as an alternative to providing a DFP is that the NRC staff agrees with the ACMUI that these amounts are adequate to cover the principal action for the complete decommissioning of sites with Ge-68/Ga-68 generators, which would be accomplished by the return of the generators to a manufacturer or distributor at the end of use. Moreover, these are the same financial assurance decommissioning funding requirements as those for possession of other non-alpha-emitting byproduct radionuclides of comparable activity based on Appendix B to Part 30.

In addition to maintaining the appropriate financial assurance, the licensee must submit and maintain for NRC inspection a legally binding agreement that ensures that the Ge-68/Ga-68 generators will be returned to the manufacturer or distributor at the end of use. Specifically, a legally binding agreement must be in place for the licensee to return these generators to the manufacturer or distributor when each generator expires and is no longer used to prepare Ga-68 radiopharmaceuticals for patients, or if the licensee ceases its use of Ga-68 radiopharmaceuticals. The legally binding agreement must highlight licensee commitments to return expired generators to the manufacturer or distributor and also must include a manufacturer or distributor commitment to accept receipt of the returned generators. The legally binding agreement shall contain terms that include:

- A commitment that the generator recipient shall return the generator to the manufacturer or distributor;
- A commitment that the generator manufacturer or distributor shall accept receipt of the returned generator;
- If conditions of the manufacturer or distributor's receipt of the generator are included in the agreement, these conditions are reasonable, are not unduly burdensome, and do not make return of the generator unreasonably onerous or impossible;
- The manufacturer or distributor is authorized to possess the radioactive material;
- The parties to the agreement are the recipient(s) of the generators and the manufacturer or distributor(s) of the generators;
- The agreement is signed by persons authorized to enter into legally binding agreements on behalf of the recipient(s) and manufacturer or distributor(s); and
- The agreement is dated.

The return of expired radionuclide generators is a well-established and preferred disposal method. It is the same method currently used to dispose of nearly every expired Mo-99/Tc-99m and Strontium-82/Rubidium-82 (Sr-82/Rb-82) generator in the United States. The return of these generators involves a simple method to ensure that the licensee will have no Ge-68 remaining at its site. The licensing staff shall use a license condition to require maintenance of the referenced legally binding agreement, and regional staff should consult with their regional counsel or the Office of the General Counsel (OGC) to confirm that an acceptable legal binding agreement is in place prior to issuing the exemption.

This exemption from 10 CFR 30.35 is granted pursuant to 10 CFR 35.19 "Specific Exemptions," which states that, "The Commission may, upon application of any interested person or upon its own initiative, grant exemptions from the regulations in this part that it determines are authorized by law and will not endanger life or property or the common defense and security and are otherwise in the public interest."

In its report (ADAMS Accession No. ML15231A047), ACMUI stated, "For a medical licensee, the foregoing regulatory considerations creates a cascade effect leading to an extensive and expensive DFP, as a DFP must cover not only the one area where a Ge-68/Ga-68 generator is used but also all areas where radioactive materials are used under the same license." In the same report, the ACMUI concluded, "The restrictive aspects arising from the current Part 30 regulations are preventing or deterring the use of promising Ga-68 diagnostic imaging agents for patients due to the decommissioning funding plan burden for its parent Ge-68."

The NRC requirements for a DFP can be costly because each DFP will need to contain a detailed decommissioning cost estimate as required by 10 CFR 30.35(e). The Ge-68/Ga-68 generator has a 12-month expiration date, and at the end of the generator's operating life, most likely it will be returned to the manufacturer or distributor for its final disposal because return of the generator is a simple method to ensure that the licensee will have no Ge-68 remaining at its site. Accordingly, the requirements of 10 CFR 30.35(e) for developing, funding, updating, and submitting detailed cost estimates for NRC review are unnecessary for the decommissioning of sites licensed for the use of Ge-68/Ga-68 generators.

As with any operation involving liquids, the elution of Ga-68 from Ge-68 generators is subject to the risk of spills. Because the eluate consists mostly of Ga-68 with a half-life of 68 minutes, the radiological contaminant of most concern is the parent, Ge-68. A small amount of Ge-68 is dissolved with the Ga-68 eluate in dilute hydrochloric acid in a phenomenon known as "breakthrough" that occurs with each elution. Ge-68 breakthrough is expressed as a percentage of total Ga-68 eluted from the column, corrected for decay. According to a peer-reviewed industry journal article, Ge-68 breakthrough is not more than 0.001 percent of the eluted Ga-68 activity. This concentration is low enough that, as the ACMUI report notes, less than two ounces (¼ cup) of sewerage are needed to dilute each elution to the concentration limit for disposal of Ge-68 in sanitary sewerage under 10 CFR 20.2003. It should also be noted that germanium is chemically similar to silicon and not apt to react under ambient conditions in a radiopharmacy.

For a number of licensees, Ge-68/Ga-68 generators will be the only radionuclide source they possess that has a half-life over 120 days (Ge- 68 has a half-life of 271 days). There are licensees, such as large research licensees, that already possess radionuclides with half-lives over 120 days (e.g., tritium H-3 with a half-life of 12.3 years and carbon C-14 with a half-life of 5730 years). In most instances, these licensees structure their possession limits so that by the ratio sum calculation, they stay within the two lower levels of financial assurances (i.e., $225,000 or $1,125,000). This structuring allows the licensee to avoid the level of financial assurance that requires a decommissioning funding plan. However, if a licensee adds one or more generators to their license, the sum of the ratios may exceed the level requiring $225,000 of financial assurance. In this case, the licensee will have to provide financial assurance in the amount of $1,125,000.

Conclusion

The most efficient and effective method to provide the needed regulatory relief from the DFP requirements for licensees who desire to possess and use Ge-68/Ga-68 generators, is to provide the NRC Regional Administrators with the authority to grant an exemption upon licensee request, for Ge-68/Ga-68 generators, if a legally binding agreement is in place for the licensee to return these generators to the manufacturer or distributor when each generator expires and is no longer used to prepare Ga-68 radiopharmaceuticals for patients, or if the licensee ceases its use of Ga-68 radiopharmaceuticals. The legally binding agreement must highlight licensee commitments to return expired generators to the manufacturer or distributor and also must include a manufacturer or distributor commitment to accept receipt of the returned generators. The NRC staff has determined that these conditions will be sufficient until a more permanent regulatory solution is reached through rulemaking.

An exemption from the 10 CFR Part 30.35 DFP requirements may be issued to any person who applies for a license to possess Ge-68/Ga-68 medical use generators, provided that the other applicable financial assurance requirements, under 10 CFR Part 30.35 are met, and the applicant submits and maintains a legally binding agreement that ensures the device will be returned to the manufacturer at the end of use. The licensing staff should use a licensing condition to require maintenance of this legally binding agreement, and the regional staff should consult with their regional counsel or OGC to confirm that an acceptable legally binding agreement is in place prior to issuing the exemption.

With Ga-68 radiopharmaceuticals, NET patients will receive lower radiation doses, and their physicians will gain superior diagnostic accuracy resulting in quicker diagnosis, earlier initiation of proper therapy, and improved patient outcomes. The NRC has determined that granting this exemption will not endanger life or property or the common defense and security and is otherwise in the public interest.

The following licensing condition should be used to allow NRC licensing staff to issue exemptions from the 10 CFR Part 30.35 DFP requirements to any licensee or applicant that applies for possession of Ge-68/Ga-68 medical use generators and that has shown it has met the requirements of 10 CFR Part 35.200 (medical facility) or 10 CFR Part 32.72 (nuclear pharmacy).

> "Notwithstanding the requirements of 10 CFR 30.35 (a)(1), the licensee is exempt from the requirement to have a decommissioning funding plan needed for the possession and use of Ge-68/Ga-68 medical use generators (make/model # of generators), based on the commitments between the licensee and manufacturer (name of manufacturer/distributor). The licensee shall return the generators to the manufacturer/distributor in accordance with the generator return agreement described in the letter/application dated _____."