



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

July 29, 2016

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

Cynthia D. Pederson, Regional Administrator
Region III

Kriss Kennedy, Regional Administrator
Region IV

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

SUBJECT: AUTHORIZATION FOR GRANTING SPECIFIC EXEMPTION
FROM DECOMMISSIONING FUNDING PLAN REQUIREMENT
FOR GERMANIUM-68/GALLIUM-68 GENERATORS

In accordance with Title 10 of the *Code of Federal Regulations* (10 CFR) Section 35.19 and Management Directive 9.26, "Organization and Functions, Office of Nuclear Material Safety and Safeguards," this memorandum is being issued to delegate to the regions the authority to grant an exemption from the decommissioning funding plan (DFP) requirements in 10 CFR 30.35(a)(1) for the possession and use of Germanium-68 (Ge-68)/Gallium-68 (Ga-68) generators, when certain conditions are met.

This memorandum authorizes the regions to issue an exemption, when requested, only as such for Ge-68/Ga-68 generators, 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 expire and are no longer used to prepare Ga-68 radiopharmaceuticals for patients, or if the licensee ceases its preparation of Ga-68 radiopharmaceuticals. The legally binding agreement between the licensee and generator manufacturer or distributor must highlight licensee commitments to return expired generators back to the manufacturer or distributor and also must include a manufacturer or distributor commitment to take expired generators back. The regions should consult with regional counsel or the Office of General Counsel (OGC) to confirm that a legal binding agreement is in place prior to issuing the exemption.

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The NRC has developed the technical basis for this exemption and the conditions under which it may be authorized. The basis and the limiting conditions are enclosed.

Concerns have been raised with respect to the resources needed to develop and maintain a DFP for Ge-68/Ga-68 generators. After careful analysis, staff agrees this DFP requirement could be an impediment and may limit patient access to the radiopharmaceuticals developed from these generators.

The Advisory Committee on the Medical Uses of Isotopes evaluated the restrictive aspects of the DFP requirement for Ge-68 that arise from 10 CFR Part 30 regulations and concluded that the subject requirement is preventing or deterring the use of promising Ga-68 diagnostic imaging agents for patients (Agencywide Documents Access and Management System Accession No. ML15231A047).

Licensing staff may issue exemptions from the 10 CFR 30.35 DFP requirements to a licensee or applicant under Part 35.200 (medical facility) or 10 CFR Part 32.72 (nuclear pharmacy) who applies for possession of Ge-68/Ga-68 medical use generators, if the licensee submits and maintains for U.S. Nuclear Regulatory Commission inspection, a legally binding agreement that ensures the device will be returned to the manufacturer or distributor at the end of use. The licensing staff shall add the following condition to the license:

“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), described in the letter/application dated _____.”

The NRC has concluded that the planned action will be sufficient to ensure public health and safety, while at the same time allowing access to the radiopharmaceuticals developed from these generators until a permanent regulatory solution is reached through rulemaking. A direct final rule process has been initiated.

Enclosure:

Technical Basis for Germanium-68
Gallium-68 Generator Decommissioning
Funding Plan Exemption and Licensing
Guidance

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“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), described in the letter/application dated _____.”

The NRC has concluded that the planned action will be sufficient to ensure public health and safety, while at the same time allowing access to the radiopharmaceuticals developed from these generators until a permanent regulatory solution is reached through rulemaking. A direct final rule process has been initiated.

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| DATE | 3/22/16 | 4/12/16 | 5/23 /16 | 6/14 /16 | 7/20/16 | 7/25/16 | 7/29/16 |

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Technical Basis for Germanium-68 Gallium-68 Generator Decommissioning Funding Plan Exemption and Licensing Guidance

Germanium-68 (Ge-68)/Gallium-68 (Ga-68) generators are widely used in Europe but are only now emerging from limited clinical trials in the U.S. They 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 being close to patients is a necessity with Ga-68's 68-minute half-life.

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) 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 found 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 and 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.

Enclosure

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 insignificant 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. The NRC staff independently verified ACMUI’s safety basis and assumptions and agrees with the recommendations in the report.

10 CFR 30.35 requires that:

(a)(1) 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 10 CFR 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.

| Ge-68 Possession Limit (millicurie [mCi])¹ | Financial Assurance required (§ 30.35) |
|--|--|
| Less than or equal to 0.1 | none |
| Greater than 0.1 to 1 | \$225,000 |
| Greater than 1 to 10 | \$1,125,000 |
| Greater than 10 | Decommissioning Funding Plan is required to determine the amount of financial assurance required |

¹ Note that these values are in mCi, (e.g. 0.1 microcurie [μ Ci] times 10^5 equals 10 mCi)

A typical new Ge-68/Ga-68 generator contains 50 mCi at its calibration date; under the NRC regulations, its possession triggers the need for a DFP. However, even with this proposed exemption, licensees must continue to provide **financial assurance** in amounts described above if they possess other radionuclides in quantities requiring a DFP. The amount would be based on their license to possess other (i.e., non Ge-68) unsealed byproduct material as described in 10 CFR 30.35(a)(1). Licensees possessing more than 2 and up to 20 Ge-68 generators (>100 to 1000 mCi) would then be subject to the requirement in § 30.35(d) for a minimum \$1,125,000 in financial assurance for the decommissioning of sites with byproduct materials in quantities with comparable risk. Licensees possessing one or two Ge-68 generators (50 to 100 mCi) would be subject to a \$225,000 minimum. The NRC staff agrees with ACMUI that these amounts are more than 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. One reason for the decision to provide for exemption request and approval is that the need for decontamination due to spills or leakage from these generators would be minimal. These are the same financial assurance decommissioning funding requirements as those for possessors 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 these 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 take expired generators back. 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 is 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 this legally binding agreement, and the regions should consult with regional their counsel or the Office of General Counsel (OGC) to confirm that a legal binding agreement is in place prior to issuing the exemption.

The NRC staff has determined that this planned action will be sufficient to ensure public health and safety until a more permanent regulatory solution is reached through rulemaking. Concurrent with this DFP exemption authority, a direct final rule process has been initiated with the aim of amending Appendix B of 10 CFR 30.35 to include the Ge-68 limit changes from 0.1 μ Ci to 10 μ Ci. This new limit will allow a licensee to use Ge-68/Ga-68 generators and not trigger the DFP requirement.

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 expressed, “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.” The same report concludes, “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 cost decommissioning 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, all 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.

The intent of this exemption is to treat all licensees equally regardless of the number of radionuclides with half-lives over 120 days on their license. For a number of licensees, Ge-68/Ga-68 generators will be the only radionuclide source with 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. Hence, for these licensees, the exemption will remove Ge-68 from the sum of the ratios calculation performed to determine the level of financial assurance (unity rule).

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 regions with the authority to grant an exemption upon licensee request, only for Ge-68/Ga-68 generators, and only 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 taking expired generators back. The NRC staff has determined that these conditions will be sufficient until a more permanent regulatory solution is reached through rulemaking.

Exemptions from 10 CFR 30.35 decommissioning financial assurance requirements may be issued to any person who applies for the possession and use of 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 licensee submits and maintains for NRC inspection a legally binding agreement that ensures the device will be returned to the manufacturer at the end of use. The licensing staff should condition the exemption of this legally binding agreement, and the regions should consult with their regional counsel or OGC to confirm that a legal 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 30.35 DFP requirements to any licensee or applicant that has shown it has met the requirements of 10 CFR Part 35.200 (medical facility) or 10 CFR Part 32.72 (nuclear pharmacy) who applies for possession of Ge-68/Ga-68 medical use generators.

“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), described in the letter/application dated _____.”