August 1, 2017

ALL AGREEMENT STATES, VERMONT, WYOMING

NOTIFICATION OF CLARIFICATION THAT GRANTING AN EXEMPTION FROM THE DECOMMISSIONING FUNDING PLAN REQUIREMENTS IN TITLE 10 OF THE CODE OF FEDERAL REGULATIONS PART 30 DOES NOT EXEMPT LICENSEES FROM OTHER FINANCIAL ASSURANCE REQUIREMENTS, UPDATE OF LICENSING GUIDANCE, AND COMPATIBILITY DETERMINATION FOR GERMANIUM-68/GALLIUM-68 GENERATORS (STC-17-057)

Purpose: To inform Agreement States that the U.S. Nuclear Regulatory Commission (NRC) staff has updated its information concerning Germanium-68 (Ge-68)/Gallium-68 (Ga-68) generators. First, the NRC staff has revised the technical basis for granting a specific exemption from the decommissioning funding plan (DFP) requirement for Ge-68/Ga-68 generators. Specifically, the technical basis clarifies that the DFP exemption does not exempt financial assurance. The enclosed memorandum (Agencywide Documents Access and Management System (ADAMS) Accession No. ML17075A487) provided to the NRC regions on July 13, 2017, updates a July 29, 2016, NRC memorandum (ADAMS Accession No. ML16082A415). Second, the Ge-68/Ga-68 generator licensing guidance has been revised to include the criteria needed for the DFP exemption. Last, the NRC staff has provided a compatibility determination for the DFP requirement.

Background: The Advisory Committee on the Medical Uses of Isotopes (ACMUI) evaluated the DFP requirement for Ge-68/Ga-68 generators that arise from Title 10 of the Code of Federal Regulations (10 CFR) Part 30 regulations and concluded that the DFP requirement was too restrictive and would prevent or deter the use of promising Ga-68 diagnostic imaging agents for patients (ADAMS Accession No. ML15231A047). The ACMUI recommended that the NRC staff exempt Ge-68/Ga-68 generator licensees from DFP requirements under certain conditions. The NRC staff analyzed the ACMUI report and agreed that the DFP requirement could impede or limit patient access to the radiopharmaceuticals developed from this generator. A typical new Ge-68/Ga-68 generator contains 50 mCi at its calibration date. Under the NRC regulations, possession of 50 mCi of Ge-68 exceeds the threshold quantity above which a DFP is required. The NRC staff determined that this exemption will ensure public health and safety and allow access to the radiopharmaceuticals developed from this generator until a permanent regulatory solution is reached through rulemaking.

Discussion: The July 29, 2016, memorandum delegated authority to the NRC regions to grant an exemption from the DFP requirement in 10 CFR Part 30 for possession and use of Ge-68/Ga-68 generators. The technical basis for the exemption relieved a licensee from the requirement for a DFP (10 CFR 30.35(a)(1)) when certain conditions were met. Specifically, the memorandum authorized the NRC regions to issue an exemption for Ge-68/Ga-68 generators when requested, only if a legally binding agreement was in place for the licensee to return the generators to the manufacturer or distributor when the generators were no longer used. The technical basis for the exemption did not remove the financial assurance requirements in 10 CFR 30.35.
The revised memorandum issued to the NRC regions on July 13, 2017, contains the technical basis for granting a specific exemption from the DFP requirement for the Ge-68/Ga-68 generators and provides (1) a clarification that granting an exemption from the DFP requirement in 10 CFR Part 30 does not exempt licensees from 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 licensing condition that specifies that the licensee must return the Ge-68/Ga-68 generators to the manufacturer or distributor when they are no longer being used.

Lastly, the enclosed revisions to the technical basis and guidance will not impact existing granted Ge-68/Ga-68 generators DFP exemptions by NRC or the Agreement States.

The NRC has updated its licensing procedure for the use of the Ge-68/Ga-68 pharmaceutical grade generator manufactured by Eckert and Ziegler Radiopharma GmbH dated July 13, 2017, (ADAMS Accession No. ML17075A488) to include items noted above.

The Standing Committee on Compatibility (SCC) has reviewed this matter and agrees that the exemption from the DFP requirements and its conditions outlined in the technical basis for licensees who possess and use Ge-68/Ga-68 generators are a matter of compatibility. An Agreement State should adopt and implement the essential objectives of this program element. With regard to meeting the financial assurance requirements in 10 CFR 30.35(b), this portion of the regulations is designated as Category Health & Safety. An Agreement State has a number of options to meet the essential objective of this requirement including:

1. Use the financial assurance monetary values from the attached technical basis document of $1,125,000 for licensees who possess more than 2 generators but less than 20 (>100 to 1000 mCi) or $225,000 in financial assurance for licensees possessing one or two Ge-68 generators (50 to 100 mCi) accompanied by a legally binding agreement for the return of the generator(s) to the manufacturer or distributor at the end of use.
2. Use the financial assurance monetary values listed in the Agreement State regulations for the quantities of Ge-68 possessed by the licensee in the generator(s) accompanied by a legally binding agreement for the return of the generator(s) to the manufacturer or distributor at the end of use.
3. Although licensees are exempt from the requirement to submit a DFP, a licensee may still choose to submit a DFP to support a different amount of financial assurance. After review and approval by the Agreement State, the licensee would provide financial assurance for the amount in the DFP.
4. Exempt their licensees from the financial assurance requirements based on a health and safety evaluation conducted and documented by the Agreement State that should include a legally binding agreement for the return of the generator(s) to the manufacturer or distributor at the end of use.

Consequently, the SCC also agrees that the licensing procedures for Ga-68/Ge-68 generators are an essential component of a licensing program and it is a matter of compatibility (see Appendix A in Compatibility Categories and Health and Safety Identification for NRC Regulations and Other Program Elements - SA-200). The NRC will review the NRC Regional and Agreement State radioactive materials programs’ implementation through the Integrated Materials Performance Evaluation Program (IMPEP) under the performance indicator, Technical Quality of Licensing Actions. An Agreement State can demonstrate meeting this compatibility requirement by implementing written procedures for the licensing of Ge-68/Ga-68...
generators that include one of the financial assurance options described above and a legally binding agreement for the return of the generator(s) to the manufacturer or distributor at the end of use if the DFP exemption is used. An example of a Ge-68/Ga-68 generator licensing guide is enclosed.

In accordance with Part VI of Management Directive 5.9 Adequacy and Compatibility of Agreement State Programs, an Agreement State must implement this requirement within 6 months of the date of this letter.

If you have any questions regarding this correspondence, please contact me at 301-415-3340 or the individuals named below:

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/RA Kevin Williams for/

Daniel S. Collins, Director
Division of Material Safety, State, Tribal and Rulemaking Programs
Office of Nuclear Material Safety and Safeguards

Enclosures:
1. Revision of Technical Basis for Granting Specific Exemption from Decommissioning Funding Plan Requirement for Germanium-68/Gallium-68 Generators
2. Eckert and Ziegler GalliaPharm™ Germanium-68/Gallium-68 Pharmacy Grade Generator Licensing Guidance, Rev. 1 (July 13, 2017)
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.

CONTACT: Said Daibes, NMSS/MSTR
(301) 415-6863
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
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 _____.”
# Table of Contents

1. 10 CFR 35.1000 Use ........................................................................................................... 1
2. Commercial Nuclear Pharmacy Use under 10 CFR 30.33 .............................................. 1
3. Licensing Guidance ........................................................................................................ 2
4. General .................................................................................................................................. 2
   4.1 Use of Eckert and Ziegler GalliaPharm™ generator to Prepare Ga-68
       Radiopharmaceuticals for Imaging and Localization Studies ..................................... 2
   4.2 Radionuclides, Form, Possession Limits, and Purpose of Use .................................. 3
   4.3 Facility Address and Description .................................................................................. 3
   4.4 Authorized Individuals ................................................................................................... 4
5. License Commitments ......................................................................................................... 5
6. Radiation Protection Program Changes ............................................................................. 7
7. Notes to Licensees .............................................................................................................. 8
   7.1 Labeling ........................................................................................................................ 8
   7.2 Survey of Dosages ......................................................................................................... 8
   7.3 Waste Disposal ............................................................................................................. 8
      7.3.1 Eluate Disposal ...................................................................................................... 8
      7.3.2 Returning Generators to the Manufacturer .......................................................... 8
   7.4 Financial Assurance for Decommissioning ................................................................. 9
      7.4.1 Specific Licensing Exemption ............................................................................... 9
8. Inspection Frequency .......................................................................................................... 10
9. Program Code ..................................................................................................................... 10
This guidance is specific to the use of the Germanium-68/Gallium-68 (Ge-68/Ga-68) pharmaceutical grade generator manufactured by Eckert and Ziegler Radiopharma GmbH (hereafter Eckert and Ziegler GalliaPharm™ generator). Future Ge-68/Ga-68 radionuclide generators will be addressed in revisions to the licensing guidance. All sections of this guidance apply to both medical licensee and commercial nuclear pharmacy licensee use of this generator unless otherwise specified. This guidance does not apply to licensees or applicants that will receive unit or bulk doses of Ga-68 radiopharmaceuticals rather than use the Eckert and Ziegler GalliaPharm™ generator themselves. These licensees and applicants will be regulated under Title 10 of the Code of Federal Regulations (10 CFR) 35.200 and, as such, authorized users (AU) must meet the requirements in 10 CFR 35.290.

1. **10 CFR 35.1000 Use**

Recently, the Food and Drug Administration (FDA) approved a Ga-68 radiopharmaceutical for diagnostic imaging of neuroendocrine tumors. Ga-68 is a positron emitter that allows Ga-68 radiopharmaceuticals to be imaged using positron emission tomography (PET). Ga-68 can be produced in a cyclotron or by the elution of a Ge-68/Ga-68 generator.

Ge-68/Ga-68 generators are similar to conventional molybdenum-99/technetium-99m (Mo-99/Tc-99m) and strontium-82/rubidium-82 (Sr-82/Rb-82) generators, which are regulated under 10 CFR 35.200. Like Mo-99/Tc-99m and Sr-82/Rb-82 generators, potential breakthrough of the parent radionuclide is possible when eluting the generator. This could lead to Ge-68 contaminating the Ga-68 radiopharmaceutical and potentially causing an unnecessarily higher radiation exposure to patients. 10 CFR 35.204 provides permissible concentration limits for parent radionuclides for Mo-99/Tc-99m and Sr-82/Rb-82 generators to limit such exposure, but no such limit is specified for Ge-68/Ga-68 generators. Therefore, the use of a Ge-68/Ga-68 generator to prepare Ga-68 radiopharmaceuticals for imaging and localization studies is regulated under 10 CFR 35.1000, 1 "Other Medical Uses of Byproduct Material or Radiation from Byproduct Material."

2. **Commercial Nuclear Pharmacy Use under 10 CFR 30.33**

Ga-68 radiopharmaceuticals may be prepared at commercial nuclear pharmacies and then provided to medical licensees for their use. Since the potential for Ge-68 breakthrough of the Eckert and Ziegler GalliaPharm™ generator exists, the U.S. Nuclear Regulatory Commission (NRC) will require appropriate commitments from applicants that use these generators prior to granting authorization to possess and use the generators to produce Ga-68. In accordance with 10 CFR 30.33, “General requirements for issuance of specific licenses,” a commercial nuclear pharmacy will have to apply for a license or amend their license in order to be authorized to possess and use the Eckert and Ziegler GalliaPharm™ generator.

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1 Medical Uses of Byproduct Material Licensed under 10 CFR 35.1000 are designated as Compatibility Category D. Agreement States are not required to adopt these regulations for purposes of compatibility.
3. Licensing Guidance

This guidance provides applicants with an acceptable means of satisfying the requirements for a license for the use of the Eckert and Ziegler GalliaPharm™ generator to prepare Ga-68 radiopharmaceuticals and is not intended to be the only means of satisfying the requirements for a license. While the Eckert and Ziegler GalliaPharm™ generator is not regulated under 10 CFR 35.200, some sections in this guidance include guidance that is analogous to provisions in 35.200. The applicant must submit the information required by 10 CFR 30.33 and 35.12, as described below. The applicant should submit additional information and commitments requested below or may, unless the information is specifically required by regulation, submit alternative information for review by the NRC staff to make a licensing determination. The commitments incorporated into the applicant’s license by license condition will be reviewed during routine inspections.

Applicants are reminded that licenses issued pursuant to 10 CFR 35.1000 must still meet the general requirements in 10 CFR Part 35, Subparts A, B, C, L, and M, except as specified in this guidance. Additionally, applicants must meet the applicable requirements of 10 CFR Parts 19, 20, and 30.

4. General

4.1 Use of Eckert and Ziegler GalliaPharm™ generator to Prepare Ga-68 Radiopharmaceuticals for Imaging and Localization Studies

Note that, per 10 CFR 35.200(b), licensees may not produce PET radionuclides, unless they also hold a Part 30 production license. However, a medical licensee may prepare its own Ga-68 radiopharmaceuticals using an Eckert and Ziegler GalliaPharm™ generator. The licensee may use the Ga-68 radiopharmaceuticals for imaging and localization studies that are prepared by either:

1) an authorized nuclear pharmacist (ANP); or
2) a physician who is an Authorized User (AU) and who meets the requirements specified in 10 CFR 35.290, or 10 CFR 35.390 and 10 CFR 35.290(c)(1)(ii)(G); or
3) an individual under the supervision, as specified in 10 CFR 35.27, of either
   a. an ANP or
   b. a physician who is an AU who meets the requirements specified in 10 CFR 35.290, or 10 CFR 35.390 and 10 CFR 35.290(c)(1)(ii)(G).

Medical licensees that prepare their own Ga-68 radiopharmaceuticals using an Eckert and Ziegler GalliaPharm™ generator may use these radiopharmaceuticals in research in accordance with a Radioactive Drug Research Committee- approved application or an Investigational New Drug (IND) protocol accepted by the FDA.

Licensees are reminded that the use of the Eckert and Ziegler GalliaPharm™ generator is regulated under 10 CFR 35.1000 and the radiopharmaceuticals produced using this generator are regulated under 10 CFR 35.200. Note that licensees that use Ga-68 radiopharmaceuticals for medical imaging and localization studies will be regulated under 10 CFR 35.200, as well. This is true whether the Ga-68 is generator- or cyclotron-produced. AUs who use Ga-68 radiopharmaceuticals must meet training requirements described in 10 CFR 35.290.
4.2  Radionuclides, Form, Possession Limits, and Purpose of Use

The applicant shall identify the radionuclides, chemical/physical form, requested maximum possession limit, and purpose of use. The NRC Form 313 must be used to submit this information. For example, the following provides the format for an acceptable request:

For medical licensees:

<table>
<thead>
<tr>
<th>Radionuclides (Form 313 Item 5)</th>
<th>Ge-68/Ga-68 as permitted by 10 CFR 35.1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical/Physical Form (Form 313 Item 5)</td>
<td>Any</td>
</tr>
<tr>
<td>Maximum Possession Limit (Form 313 Item 5)</td>
<td>100 mCi of Ge-68</td>
</tr>
<tr>
<td></td>
<td>100 mCi of Ga-68</td>
</tr>
<tr>
<td>Authorized Use (Form 313 Item 6)</td>
<td>For 10 CFR 35.1000 use of the Eckert and Ziegler GalliaPharm™ generator to prepare Ga-68 radiopharmaceuticals for imaging and localization studies.</td>
</tr>
<tr>
<td></td>
<td>Any imaging and localization study permitted by 10 CFR 35.200.</td>
</tr>
</tbody>
</table>

For commercial nuclear pharmacy licensees:

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>Ge-68</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ga-68</td>
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<tr>
<td>Chemical/Physical Form (Item 5)</td>
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<tr>
<td>Maximum Possession Limit (Item 5)</td>
<td>100 mCi of Ge-68</td>
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<tr>
<td></td>
<td>100 mCi of Ga-68</td>
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<tr>
<td>Authorized Use (Form 313 Item 6)</td>
<td>For use of the Eckert and Ziegler GalliaPharm™ generator to prepare Ga-68 radiopharmaceuticals for imaging and localization studies.</td>
</tr>
<tr>
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<td>For preparation and distribution of radioactive drugs in accordance with 10 CFR 32.72 and radiochemicals for non-medical use to authorized recipients.</td>
</tr>
</tbody>
</table>

Note Ga-68 eluent is not a radioactive drug until it has been prepared in accordance with an FDA accepted IND application or an FDA approved New Drug application (NDA). Prior to preparation, the Ga-68 eluent is considered a radiochemical.

4.3  Facility Address and Description [10 CFR 30.33(a)(2) and 10 CFR 35.12(b)(1)]:

Provide an address of use and submit a facility diagram and description of the location(s) where the generator will be received, used, and stored. If applicable, provide a description of imaging
rooms and patient waiting rooms and include shielding information and calculations appropriate for the PET facility. American Association of Physicists in Medicine Task Group 108, “PET and PET/CT Shielding Requirements,” provides guidance on how to design a PET facility and perform associated shielding calculations. Additional information can also be found in NUREG 1556 Volume 9, Revision 2.

4.4 Authorized Individuals [10 CFR 30.33(a)(3) and 10 CFR 35.12(b)(1)]:

The NRC has determined that individuals meeting the guidance provided below will be considered qualified and authorized to use the Eckert and Ziegler GalliaPharm™ generator to develop/create Ga-68. Applicants may also submit alternative training and experience commitments to be reviewed on a case-by-case basis by the NRC staff. The alternative information should include an explanation of why the applicant believes the alternative information demonstrates that an individual is qualified to be an AU or ANP.

Identify each AU or ANP and provide documentation of his/her training and experience in the use of the Eckert and Ziegler GalliaPharm™ generator. NRC Form 313A (AUD), “Authorized User Training and Experience and Preceptor Attestation for uses defined under 10 CFR 35.200 and 35.300,” and NRC Form 313A (ANP), “Authorized Nuclear Pharmacist Training and Experience and Preceptor Attestation [10 CFR 35.55]” or other formats may be used to document this training and experience. The individual will be considered qualified for use of the Eckert and Ziegler GalliaPharm™ generator if the licensee demonstrates that the individual meets the following:

1) Is currently listed on a license or permit (NRC, Agreement State, or Broad Scope License, or a permit issued by a NRC Master Materials Licensee) as an ANP under 10 CFR 35.55, “Training for an authorized nuclear pharmacist;”

   OR

2) Is currently listed on a license or permit (NRC, Agreement State, Broad Scope License or NRC Master Materials License) as an AU for 10 CFR 35.200, “Use of unsealed byproduct material for imaging and localization studies for which a written directive is not required;” or is certified by a recognized medical specialty board listed on NRC’s Web site under 10 CFR 35.290, “Training for imaging and localization studies;”

   OR

3) Is currently listed on a license or permit (NRC, Agreement State, Broad Scope License or NRC Master Materials License) as an AU under 10 CFR 35.390 and meets the requirements in 10 CFR 35.290(c)(1)(ii)(G);

   OR

4) Has completed 700 hours of training and experience, including a minimum of 80 hours of classroom and laboratory training, in basic radionuclide handling techniques applicable to the medical use of unsealed byproduct material for imaging and localization studies. The training and experience must include, at a minimum:
(i) Classroom and laboratory training in the following areas—
   (A) Radiation physics and instrumentation;
   (B) Radiation protection;
   (C) Mathematics pertaining to the use and measurement of radioactivity;
   (D) Chemistry of byproduct material for medical use;
   (E) Radiation biology; and

(ii) Work experience, under the supervision of an AU who meets the
    requirements in 10 CFR 35.57, 35.290, or 35.390 and 35.290(c)(1)(ii)(G),
    involving—
    (A) Ordering, receiving, and unpacking radioactive materials safely and
        performing the related radiation surveys;
    (B) Performing quality control procedures on instruments used to determine
        the activity of dosages and performing checks for proper operation of
        survey meters;
    (C) Calculating, measuring, and safely preparing patient or human research
        subject dosages;
    (D) Using administrative controls to prevent a medical event involving the use
        of unsealed byproduct material;
    (E) Using procedures to safely contain spilled radioactive material and using
        proper decontamination procedures;
    (F) Administering dosages of radioactive drugs to patients or human research
        subjects; and
    (G) Eluting generator systems appropriate for preparation of radioactive
        drugs for imaging and localization studies, measuring and testing the
        eluate for radionuclidic purity, and processing the eluate with reagent kits
        to prepare labeled radioactive drugs.

AND

Has obtained written attestation, signed by a preceptor AU who meets the
requirements in 10 CFR 35.57, 35.290, 35.390 and 35.290(c)(1)(ii)(G), or 35.1000
Ge-68 generator use, that the individual has satisfactorily completed the
requirements in this section and is able to independently fulfill the radiation
safety-related duties as an AU for the authorized use of the Eckert and Ziegler
GalliaPharm™ generator. The written attestation is not required for individuals who
hold certification by a recognized specialty board.

Physicians or nuclear pharmacists, working under supervision of an AU or ANP described
above, are authorized to elute the Eckert and Ziegler GalliaPharm™ generator to prepare Ga-68
radiopharmaceuticals for imaging and localization studies in accordance with 10 CFR 35.27.

5. **License Commitments**

An applicant requesting authorization for the Eckert and Ziegler GalliaPharm™ generator shall
commit to the following:

- Providing instructions and/or training on the manufacturer’s procedures to all individuals
  involved in Ge-68/Ga-68 generator use, commensurate with the individual’s duties to be
  performed;
• Not to opening, breaching, or physically modifying the Eckert and Ziegler GalliaPharm™ generator in any way;

• Following the manufacturer’s procedures, including: generator set-up; generator elution; drug preparation; Ge-68 breakthrough testing; and final disposition;

• To eluting the generator in accordance with the manufacturer’s stated frequency and procedures to minimize the concentration of Ge-68 in the eluate;

• Not using an expired generator for preparation of materials that will be administered to patients or human research subjects;

• Only using a generator that has a clearly marked expiration date;

• After installation, eluting the generator and properly disposing of the eluate prior to the first use of eluate for testing or human use;

• Developing and implementing written procedures for the determination of breakthrough that will detect whether the eluate exceeds the manufacturer’s 0.001 percent breakthrough limit, i.e., the presence of Ge-68 in excess of a ratio of 0.01 µCi Ge-68 per 1 mCi Ga-68;

• Not knowingly administer to a patient or human research subject any material containing Ga-68 which is determined to exceed the manufacturer’s 0.001 percent breakthrough limit;

• If the generator has not been eluted within 48 hours, then discarding the first eluate prior to use (e.g., if the generator is used Friday and the next elution is not until Monday morning then the first eluate shall be discarded);

• Measuring the breakthrough of the generator at least once every 7 calendar days when in use;

• Removing a generator from use if the measured Ge-68 breakthrough exceeds the manufacturer’s stated breakthrough limit;

• Not returning a generator to service until the breakthrough has been measured again in a new elution and determined to be below the manufacturer’s stated breakthrough limit.

• Maintaining a record of the breakthrough tests for at least 3 years. These tests should include the ratio of the measured activity of Ge-68 per Ga-68 corrected for the time of elution, time and date of the elution, time and date of the measurement, and the name of the individual who made the measurement;

• Developing and implementing written emergency procedures for leaking or damaged generators;

• Notifying by telephone the NRC Operations Center (301-816-5100) and the manufacturer/distributor of the generator within 7 calendar days after discovery of an
eluate (excluding eluates from flushing the generator in accordance with manufacturer procedures) that exceeded the manufacturer’s stated breakthrough limits of Ge-68;

• Include in the report to the NRC Operations center the manufacturer, model number, and serial number (or lot number) of the generator; the results of the measurement; the date of the measurement; whether dosages were administered to patients or human research subjects; when the manufacturer/distributor was notified; and the action taken;

• Reporting, in writing, within 30 days of a failed breakthrough calculation in accordance with the rules for medical events, and reportable events as applicable;

• Sending a written report to the appropriate NRC Regional Office within 30 days after discovery of an eluate (excluding eluates from flushing the generator in accordance with manufacturer procedures) that exceeded the manufacturer’s stated breakthrough limits of Ge-68. Include in the written report the action taken by the licensee; the patient dose assessment; the methodology used to make this dose assessment if the eluate was administered to patients or human research subjects; probable cause and assessment of failure in the licensee's equipment, procedures or training that contributed to the excessive readings if an error occurred in the licensee's breakthrough determination, and the information in the telephone report made as described above;

• Wipe testing all areas of licensed material use, including the generator storage and kit preparation areas, for contamination each day of use; and

• Wipe testing the generator casing quarterly for expired or unused generators in storage for more than 3 months.

6. **Radiation Protection Program Changes** [10 CFR 35.26]

An applicant initially applying for authorization for use of the Eckert and Ziegler GalliaPharm™ generator for preparation of Ga-68 radiopharmaceuticals for imaging and localization studies may request to incorporate into its license a change process similar to 10 CFR 35.26. Such a change process can allow some future changes to radiation safety programs provided that the change process requires the following conditions to be met for revisions to the radiation protection program:

1. The revision does not require a license amendment under 10 CFR 35.13;

2. The revision is based upon NRC’s current guidance for use of the Eckert and Ziegler GalliaPharm™ generator to prepare Ga-68 radiopharmaceuticals for imaging and localization studies under 10 CFR 35.1000 posted on the NRC Medical Uses Licensee Toolkit;

3. The revision has been reviewed and approved by the licensee’s Radiation Safety Officer and management;

4. The affected individuals are instructed on the revised program before the change is implemented;

5. The licensee shall retain a record of each change for 5 years; and
6. The record will include a copy of the current guidance for use of the Eckert and Ziegler GalliaPharm™ generator to prepare Ga-68 radiopharmaceuticals for imaging and localization studies under 10 CFR 35.1000, the old procedure, the new procedure, the effective date of the change, and the signature of the licensee management representative who reviewed and approved the change.

If approved, these conditions for use of updated guidance will be incorporated as license conditions in the licensee’s license.

7. Notes to Licensees

7.1 Labeling

Syringes and unit dosages must be labeled in accordance with 10 CFR 35.69 for medical licenses and 10 CFR 32.72(a)(4) for commercial nuclear pharmacy licenses.

7.2 Survey of Dosages

Assay each patient dosage in the dose calibrator (or instrument) before administering it (10 CFR 35.63). Do not use a dosage if it does not fall within the prescribed dosage range or if it varies more than ±20 percent from the prescribed dosage, except as approved by an AU.

7.3 Waste Disposal

7.3.1 Eluate Disposal

Due to breakthrough, the eluate may contain small amount of Ge-68 activity, which has a half-life of greater than 120 days (the half-life of Ge-68 is 270.8 days). Depending on the activity of Ge-68, composition of the waste, and state, local, and federal regulations, the licensee may need to:

- Dispose the waste in accordance with 10 CFR 20.2003. Please note that the waste generated during elution and dose preparation is acidic. For final disposal, the acidic solution may need to be placed into a chemical waste container; or

- Transfer the waste to an authorized recipient.


7.3.2 Returning Generators to the Manufacturer

Used generators may be returned to the manufacturer. This permission does not relieve licensees from the requirement to comply with 10 CFR Part 71 and Department of Transportation (DOT) regulations. Perform the following actions when returning the Eckert and Ziegler GalliaPharm™ generator:
• Retain the records needed to demonstrate that the package qualifies as a DOT Specification 7A container.
• Assemble the package in accordance with the manufacturer’s instructions.
• Perform the dose-rate and removable-contamination measurements.
• Label the package and complete the shipping papers in accordance with the manufacturer’s instructions.
  Retain records of receipts and transfers in accordance with 10 CFR 30.51, “Records.”

7.4 Financial Assurance for Decommissioning

7.4.1 Specific Exemptions

In accordance with 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. In a July 29, 2016, memorandum (Agencywide Documents Access and Management Accession No. ML16082A415) the Director of the NRC Office of Nuclear Material Safety and Safeguards delegated to the NRC’s Regional Administrators the authority to grant an exemption to the DFP requirement in 10 CFR Part 30 for possession and use of Ge-68/Ga-68 generators under certain circumstances.

The revised memorandum issued on July 13, 2017 (Accession No. ML17075A487) specifically authorizes the Regional Administrators to issue an exemption, when requested, only for Ge-68/Ga-68 generators and only if a legally binding agreement was in place for the licensee to return the generators to the manufacturer or distributor when the generators were no longer used. Licensees must continue to provide FA in amounts described in the exemption memorandum. Licensees possessing one or two Ge-68/Ga-68 generators (50 to 100 mCi) must provide for financial assurance for decommissioning in the amount of $225,000.00. Licensees possessing more than 2 generators (>100 mCi) must provide for financial assurance for decommissioning in the amount of $1,125,000.00.

The legally binding agreement should contain terms that include: (1) a commitment that the generator recipient shall return the generator to the manufacturer or distributor; (2) a commitment that the generator manufacturer or distributor shall accept receipt of the returned generator; (3) if conditions of the manufacturer or distributor’s receipt of the generator are included in the agreement, these conditions are reasonable, do not appear unduly burdensome, and do not appear to make return of the generator unreasonably onerous or impossible; (4) the manufacturer or distributor is authorized to possess the radioactive material; (5) the parties to the agreement are the recipient(s) of the generators and the manufacturer or distributor(s) of the generators; (6) 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 (7) the agreement is dated.
Licensees and applicants who wish to request such an exemption should refer to the exemption memorandum for more information.

8. **Inspection Frequency**

Licensees authorized to use an Eckert and Ziegler GalliaPharm™ generator to prepare Ga-68 radiopharmaceuticals should be inspected every 5 years. Per Enclosure 1 to Inspection Manual Chapter (IMC) 2800, licenses authorizing emerging technology in 10 CFR 35.1000 for diagnostic use are assigned a Priority 5 inspection code.

The commercial nuclear pharmacy licensees authorized to use the Eckert and Ziegler GalliaPharm™ generator will also be inspected every 2 years. This is the normal inspection frequency for a commercial nuclear pharmacy.

9. **Program Code**

In accordance with IMC 2800, program codes 02121, 02201, and 02220 are for a “medical institution – written directive not required.” The use of Ga-68 radiopharmaceuticals that are produced using the Eckert and Ziegler GalliaPharm™ generator under 10 CFR 35.1000 is a diagnostic use that does not require a written directive. Therefore, the NRC regions should use program code 02121, 02201, or 02220, as applicable.

The commercial nuclear pharmacies will continue to use the program code 02500.
Paperwork Reduction Act Statement

The information collections contained in this draft guidance are covered by the requirements of 10 CFR Parts 30 and 35, which were approved by the Office of Management and Budget (OMB), approval numbers 3150-0017, 3150-0120 and 3150-0010.

Public Protection Notification

The NRC may not conduct or sponsor, and a person is not required to respond to, a request for information or an information collection requirement unless the requesting document displays a currently valid OMB control number.
## SUBJECT: ECKERT AND ZIEGLER GALLIAPHARM\textsuperscript{TM} GERMANIUM-68/GALLIUM-68 PHARMACY GRADE GENERATOR LICENSING GUIDANCE

### ML17075A488

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