Eckert and Ziegler GalliaPharm™ Germanium-68/Gallium-68 Pharmacy Grade Generator

Licensing Guidance

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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.

[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:

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

For commercial nuclear pharmacy licensees:

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

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. <u>Radiation Protection Program Changes</u> [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.

Additional information can also be found in reference IN 94-07, "Solubility Criteria for Liquid Effluent Releases to Sanitary Sewerage Under the Revised 10 CFR Part 20," dated January 28, 1994.

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™ GERMANIUM-68/GALLIUM-68 PHARMACY GRADE GENERATOR LICENSING GUIDANCE

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