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

November 13, 2016

MEMORANDUM TO: Philip O. Alderson, M.D., Chairman
Advisory Committee on the Medical Uses of Isotopes

FROM: Daniel S. Collins, Director ***/RA/ PHenderson for DCollins***
Division of Material Safety, State, Tribal,
and Rulemaking Programs
Office of Nuclear Material Safety
and Safeguards

SUBJECT: RESPONSES TO THE ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES' AUGUST 25, 2016 RECOMMENDATIONS ON THE ECKERT AND ZIEGLER GALLIAPHARM™ GERMANIUM-68/GALLIUM-68 PHARMACY GRADE GENERATOR LICENSING GUIDANCE

Below are the staff responses to the recommendations from the August 25, 2016 Advisory Committee on the Medical Uses of Isotopes (ACMUI) Final Report (ML16238A311) on their review of the Eckert and Ziegler Gallipharm™ Germanium-68/Gallium-68 Pharmacy Grade Generator Licensing Guidance. The Committee provided six recommendations, five of which were accepted and one that was partially accepted by the U.S. Nuclear Regulatory Commission (NRC) staff. They are the following:

1. **ACMUI Recommendation:** The Committee recommended that the section entitled, "Licensing Guidance," be re-named, "Purpose," and re-located to the beginning of the Guidance (i.e., immediately following the Table of Contents). An explicit statement such as the following should be included, "This Guidance provides applicants with an acceptable means of satisfying the requirements for a license for the use of a column based Ge-68/Ga-68 generator for producing Ga-68 to be used in the preparation of Ga-68 radiopharmaceuticals."

   Staff Response: Partially Accepted. The NRC staff agreed with including an explicit purpose statement and has incorporated it with minor modifications into the section entitled, "Licensing Guidance." The statement included states the following:

   > "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."

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The NRC staff did not accept the recommendation to rename or relocate the section. The proposed change is contrary to the standard formatting and language that has been approved for these types of licensing guidance documents. Specifically, the section titled, "Licensing Guidance," explains that the licensing guidance document provides applicants with acceptable means to obtain a materials license for that use, but is not the only means for satisfying the requirements for a license. The section that immediately follows the Table of Contents is titled, "10 CFR 35.1000." That section is the first section of the guidance because it defines why a particular medical technology is being licensed under Title 10 *Code of the Federal Regulations* (10 CFR) 35.1000.

2. **ACMUI Recommendation:** The Committee recommended providing clarification of what is regulated under 10 CFR 35.200 and 10 CFR 35.1000. The guidance should state that the regulation of Ga-68 radiopharmaceuticals under 10 CFR 35.200 applies to patient dosages obtained from appropriately trained authorized users or authorized nuclear pharmacists within a medical facility as well as from commercial nuclear pharmacies. Accordingly, the Committee recommended revisions of the passage in lines 73-84 on page 2 of the Licensing Guidance, including the section entitled, "Commercial Nuclear Pharmacy User under 10 CFR 30.33," as follows:

   Use of Ga-68 Radiopharmaceuticals

   Please note that licensees that use unit dosages of Ga-68 radiopharmaceuticals for medical imaging and localization studies will be regulated under 10 CFR 35.200 and authorized users (AUs) must comply with the requirements of 10 CFR 35.290. The licensee may use a Ga-68 radiopharmaceutical that is prepared from the elution of a Ge-68/Ga-68 generator for medical use for imaging and localization studies that is either:

   1) Obtained in a manner described in 10 CFR 35.200 (c) or (d);
   2) Obtained from a manufacturer or preparer licensed under 10 CFR 32.72 or equivalent Agreement State requirements and has made commitments as described in this guidance; or,
   3) Prepared by an authorized nuclear pharmacist (ANP); a physician who is an AU who meets the requirements of this license guidance and the requirements specified in 10 CFR 35.290, or 10 CFR 35.390 and 10 CFR 35.290(c)(1)(ii)(G); or an individual under the supervision, as specified in 10 CFR 35.27, of the ANP or the physician who is an AU and have made commitments as described in this guidance.

   Licensees that use cyclotron-produced Ga-68 radiopharmaceuticals for medical imaging and localization studies will be regulated under 10 CFR 35.200 and AUs must meet 10 CFR 35.290.

   Staff Response: Accepted. The NRC staff has accepted the Committee's recommendation by adding a statement at the beginning of the guidance document that states the following:

   > "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 Ecker and Ziegler GalliaPharm™ generator themselves. These licensees and applicants will be regulated under 10 CFR 35.200 and, as such, authorized users (AU) must meet the requirements in 10 CFR 35.290."

Section 4.1 of the licensing guidance denotes who may prepare the Ga-68 radiopharmaceuticals. It also includes a note that states that licensees who use Ga-68 radiopharmaceuticals for medical imaging and localization studies, regardless of if they're generator- or cyclotron-produced, will be regulated under 10 CFR 35.200.

3. **ACMUI Recommendation:** The Committee recommended modifying the language in the "Use of Ge-68/Ga-68 Generators" Section to the following language:

Use of Ge-68/Ga-68 Generators

Recently, the FDA approved a gallium-68 (Ga-68) radiopharmaceutical for diagnostic imaging of somatostatin receptor (SSR)-positive neuroendocrine tumors. Ga-68 is a positron emitter which allows Ga-68 radiopharmaceuticals to be imaged using positron emission tomography (PET) in a manner similar to fluorine-18 (F-18) radiopharmaceuticals. Ga-68 produced in a cyclotron, like F-18, may be used to produce Ga-68 radiopharmaceuticals for use under 10 CFR 35.200. However, unlike F-18, Ga-68 can also be produced from the elution of a Ge-68/Ga-68 generator to prepare Ga-68 radiopharmaceuticals. As such, the Ge-68/Ga-68 generator eluate generally cannot be used directly in patients for imaging, but only as a precursor for the preparation of Ga-68-labeled radiopharmaceuticals.

Staff Response: Accepted. The NRC staff has accepted the Committee's recommendation with modifications under the section titled, "10 CFR 35.1000 Use." Specifically, the text states:

"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. This guidance is specific only to the Eckert and Ziegler GalliaPharm™ generator. Future Ge-68/Ga-68 radionuclide generators will be addressed in revisions to the licensing guidance."

4. **ACMUI Recommendation:** The Committee recommended modifying the language in the "Authorized Individuals" Section to the following language:

4) Meets the criteria under 10 CFR 35.290, "Training for imaging and localization studies;" AND
5) Has completed the following training in the use of a Ge-68/Ga-68 generator for producing Ga-68 radiopharmaceuticals for 35.200 use:

a. elution and quality control procedures needed to determine Ga-68 activity and Ge-68 breakthrough levels appropriate for the preparation of radiopharmaceuticals for imaging and localization studies;

b. measuring and testing the eluate for radionuclidic purity; and
c. safety procedures for the use of the Ge-68/Ga-68 generator.

Staff Response: Accepted. The NRC staff has accepted this recommendation with modifications under the section titled "Authorized Individuals."

5. **ACMUI Recommendation:** The Committee recommended modifying the language in the "Training for individuals other than AUs and ANPs" section to the following language:

   Training for individuals others than AUs and ANPs

   The applicant shall commit to provide training in the licensee's procedures to all individuals involved in Ge-68/Ga-68 generator use for the production of Ga-68 radiopharmaceuticals for 35.200 use, commensurate with the individual's duties to be performed. This training must be provided to all individuals eluting the generator or preparing, or measuring the Ga-68 unit dose.

   Staff Response: Accepted. The NRC staff has accepted this recommendation with modifications and has incorporated the text in the section titled "License Commitments." Specifically, the text states the following:

   > "Provide instructions and/or training on the manufacturer's procedures to all individuals involved in the Ge-68/Ga-68 generator use, commensurate with the individual's duties to be performed."

6. **ACMUI Recommendation:** The Committee recommended modifying the language in the "Radiation Protection Program Changes" section to the following language:

   This guidance may be revised as additional experience is gained regarding the use of a Ge-68/Ga-68 generator for preparation of Ga-68 radiopharmaceuticals for 35.200 use. An applicant initially applying for authorization for use of Ge-68/Ga-68 generator under this 35.1000 use 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 without the need to amend the license to radiation safety programs provided that the change process requires the following conditions to be met for revisions to the radiation safety program:

   Staff Response: Accepted. The NRC staff has accepted this recommendation with minor modifications to reflect that the guidance is specific to the Eckert and Ziegler GalliaPharm™ Ge-68/Ga-68 Pharmacy Grade Generator and has incorporated the new language in the section entitled "Radiation Protection Program Changes."

When the NRC staff provided the Committee with the draft licensing guidance document for their review, it was broadly applied to any Ge-68/Ga-68 medical generator. Since then, the NRC staff decided to narrow the scope of the guidance to only include the Eckert and Ziegler GalliaPharm™ Ge-68/Ga-68 Pharmacy Grade Generator because it was the only generator to have received FDA approval. It will be updated in the future to include other Ge-68/Ga-68 generators as they are approved by FDA. The NRC staff issued the "Eckert and Ziegler Galliapharm™ Germanium-68/Gallium-68 Pharmacy Grade Generator Licensing Guidance" on October 17, 2016 (ML16287A403).

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