Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Use of Isotopes (ACMUI)

Sub-Committee on
Germanium-68/Gallium-68 Generator Licensing Guidance

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Introduction

The Unites States Food and Drug Administration (FDA) recently approved a gallium-68 (Ga-68) radiopharmaceutical, Ga-68-DOTATATE, for diagnostic imaging by positron emission tomography (PET) of somatostatin receptor-positive tumors. In contrast to most positron-emitting radioisotopes, Ga-68 can be produced by a radionuclide generator, the germanium-68/gallium-68 (Ge-68/Ga-68) generator, rather than a cyclotron. The Nuclear Regulatory Commission (NRC) in conjunction with Agreement-State representatives has drafted guidance to provide applicants with an acceptable means of satisfying the regulatory requirements for a license for the use of a Ge-68/Ga-68 generator for producing Ga-68 to be used in the preparation of Ga-68-labeled radiopharmaceuticals. The NRC Advisory Committee on the Medical Use of Isotopes (ACMUI) subsequently convened a Sub-Committee to review and comment on this Licensing Guidance; this document represents the Sub-Committee's report on this Guidance. In this report, relevant sections of 10 CFR35 are included in an Appendix.

Background

Neuroendocrine tumors (NETs) present a difficult diagnostic challenge in clinical oncology. For example, by conventional methods it currently takes on average seven years for definitive diagnosis of and delivery of appropriate therapy to a NET. The FDA recently approved Netspot™[1], a sterile, single-dose kit for preparation of Ga-68-DOTATATE (or DOTA-octreotate) injection for intravenous use. Ga-68-DOTATATE is the first approved radiopharmaceutical among a new class of agents for diagnostic imaging of NETs[2]. It consists of the positron-emitting radioisotope Ga-68

[1] Netspot™ Package Insert. NETSPOT (kit for the preparation of gallium Ga68 dotatate injection) for intravenous use, Reference ID: 3939719. Manufactured by Gipharma Srl (Saluggia (Vc), Italy), Distributed by Advanced Accelerator Applications USA, Inc (New York, NY), June 2016.

[2] Breeman WAP, De Blois E, Sze Chan H, Konijnenberg M, Kwekkeboom DJ, Krenning EP. ^{68}Ga-labeled DOTA-peptides and ^{68}Ga-labeled radiopharmaceuticals for positron emission tomography: Current status of research, clinical applications, and future perspectives. Sem Nucl Med 41: 314–321, 2011.

labeled, via the DOTA[3] chelator, to the somatostatin receptor (SSR)-binding peptide octreotate. The important diagnostic advantages of such agents are illustrated in Figure 1[4], juxtaposing images of indium-111 (In-111)-DTPA[5]-octreotide (In-111-octreotide)[6] (left panel) and Ga-68-DOTATOC (or (DOTA^0-Phe^1-Tyr^3)octreotide)[7,8] (right panel). Until the approval of Netspot™ and Ga-68-DOTATATE, In-111-octreotide was the only available radiopharmaceutical for diagnostic imaging of NETs. Ga-68-labeled SSR-binding agents compared to In-111-octreotide imaging clearly provide superior sensitivity and superior spatial and contrast resolution. Further, Ga-68-DOTATOC and-DOTATATE not only provide more favorable radiation dosimetry (with effective doses of 2.3 mSv versus 11 mSv, respectively, for Ga-68 and In-111) but are also more convenient for patients than In-111-octreotide, allowing same-day imaging rather than adding a second visit for imaging at 24 hours after radiopharmaceutical injection. The introduction of Ga-68-DOTATATE will thus result in far more reliable and more convenient diagnosis and more timely treatment of NETs.

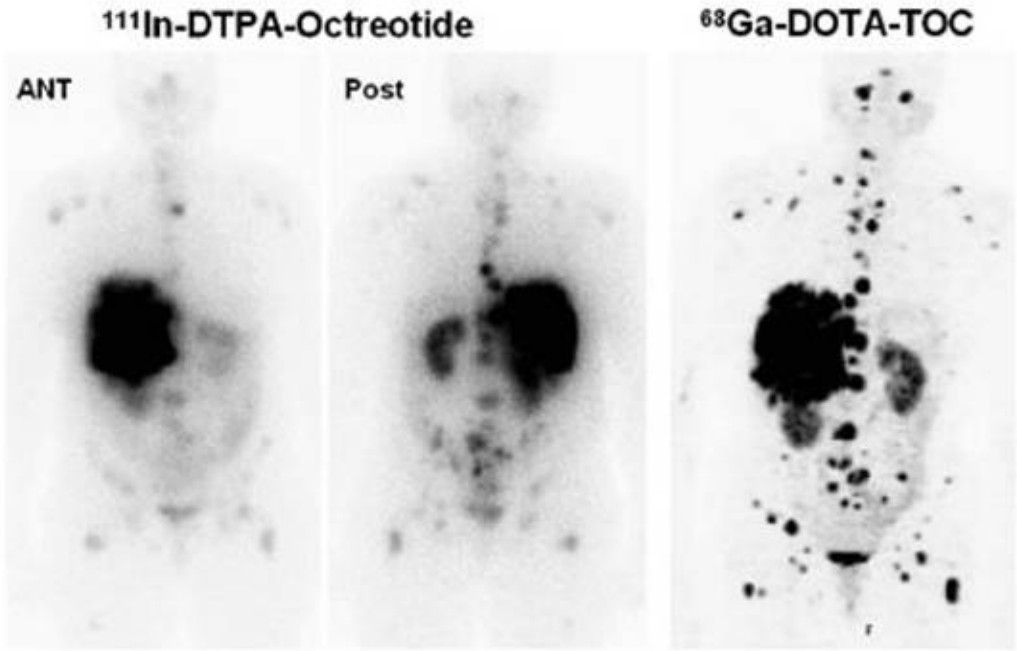

Figure 1. Coronal (i.e., anterior and posterior) planar gamma-camera images of a patient with metastatic NETs acquired using In-111-octreotide (left panel). Coronal PET image of the same patient acquired using Ga-68-DOTATOC.

[3] 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid

[4] Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, Von Guggenberg E, Bale R, Virgolini IJ. ^{68}Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: Comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 48: 508-518, 2007.

[5] diethylenetriaminepentaacetic acid

[6] Kwekkeboom DJ, Krenning EP. Somatostatin receptor imaging. Sem Nucl Med 32: 84–91, 2002

[7] DOTATOC is a structural analog of DOTATATE with a slightly lower binding affinity for the SSR.

[8] Bushnell DL, O'Dorisio TM, O'Dorisio MS, Menda Y, Hicks RJ, Van Cutsem E, Baulieu, JL, Borson-Chazot F, Anthony L, Benson AB, Oberg K, Grossman AB, Connolly M, Bouterfa H, Li Y, Kacena KA, Lafrance N, Pauwels SA). ^{90}Y-Edotreotide for metastatic carcinoid refractory to octreotide. J Clin Oncology 28: 1652–1659, 2010.

Ga-68 is a short-lived (physical half-life: 68 minutes), positron-emitting radiometal which can be produced in a cyclotron or, more commonly, in the Ge-68/Ga-68 generator, similar to the familiar molybdenum-99/technetium-99m (Mo-99/Tc-99m) generator. The parent radionuclide, Ge-68, is relatively long-lived (physical half-life: 271 days) and therefore this generator can, in principle, provide Ga-68 for an extended period of time in excess of 1 year; in practice, however, the shelf-life of such generators is currently specified as 1 year from the date of calibration[9]. Further, through chelation chemistry, Ga-68 can be used to radiolabel a wide variety of antibodies and antibody fragments as well as peptides and thus can provide PET radiopharmaceuticals with broad applications beyond NETs[10]. The potential impact of the Ge-68/Ga-68 generator in molecular imaging therefore is significant and the timely dissemination of practical regulatory guidance for the licensing and safe use of these generators is therefore needed to ensure physician and patient access to these new and promising diagnostic radiopharmaceuticals. This led to the development of the NRC's draft Ge-68/Ga-68 Generator Licensing Guidance; the ACMUI review of this Guidance is the subject of this Report.

As with any radionuclide generator such as conventional molybdentum-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[11], the parent radionuclide in the Ge-68/Ga-68 generators, Ge-68, can potentially breakthrough when eluting the Ga-68 from the generator. Such breakthrough and the resulting Ge-68 contamination of the Ga-68-labeled radiopharmaceutical prepared using the eluate can result in avoidable radiation doses to patients receiving the Ge-68-contaminated Ga-68-labeled radiopharmaceutical. 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 exposures, but does not provide such a concentration limit for Ge-68/Ga-68 generators. As a result, according to the License Guidance the use of Ga-68 eluted from a Ge-68 generator to prepare Ga-68 radiopharmaceuticals for imaging and localization studies must be regulated under 10 CFR 35.1000, "Other Medical Uses of Byproduct Material or Radiation from Byproduct Material" rather than 10 CFR 35.200, "Use of Unsealed Byproduct Material for Imaging and Localization Studies for which a Written Directive is Not Required." It should be emphasized that the additional radiation dose to patients resulting from Ge-68 breakthrough when eluting a Ge-68/Ga-68 generator is extremely low, as demonstrated by the following analysis. According to Sunderland et al[12], Ge-68 breakthrough is ~0.5 nCi Ge-68/mCi Ga-68. For quantitative elution of 50-mCi generator (i.e, elution of 50 mCi of Ga-68), the maximum breakthrough would be 25 nCi = 0.025 μCi Ge-68. According to Velikyan et al[13], the gender-averaged effective dose for intravenously injected Ge-68

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[9] GalliaPharm Pharmaceutical GMP Grade ^{68}Ge/^{68}Ga-Generator: Instructions for Use, Revision 1.4. Eckert & Ziegler Radiopharma GmbH, Berlin, Germany, May 27, 2016.

[10] Rosch F. ^{68}Ge/^{68}Ga generators and ^{68}Ga radiopharmaceutical chemistry on their way into a new century. J Postgrad Med Edu Res 47: 18-25, 2013.

[11] The sections of the Code of Federal Regulations (CFR) cited in this Report are included as an Appendix.

[12] Sunderland J, Dick D, Schultz M, Gordon Watkins G, Sensoy L. Quantitative assessment of Ge068 breakthrough from a commercial titanium-dioxide based Ge-68/Ga-68 generator. J Nucl Med 54 (Suppl 2): 1186, 2013.

[13] Velikyan I, Antoni G, Jens Sörensen J, Sergio Estrada S. Organ biodistribution of germanium-68 in rat in the presence and absence of [^{68}Ga]Ga-DOTA-TOC for the extrapolation to the human organ and whole-body radiation dosimetry. Am J Nucl Med Mol Imaging 3: 154-165, 2013.

is 13 μSv/MBq = 0.048 mrem/μCi, yielding a total effective dose of 0.025 μCi • 0.048 mrem/μCi = 0.0012 mrem. Even if one conservatively assumed a 100-fold greater Ge-68 breakthrough than that reported by Sunderland et al., the additional effective dose to the patient would be 0.12 mrem. In comparison, the maximum permissible dose to the general public, 100 millirem/year, is approximately 10,000-fold greater. The actual Ge-68 activity in the Ga-68 radiopharmaceutical preparation would be reduced further by the radiochemical procedure (including the use of guard columns to "trap" Ge-68 in the eluate) used for the preparation of the radiopharmaceutical. As noted, therefore, the additional radiation dose to a patient from Ge-68 breakthrough would be trivial.

The current breakthrough limit, 0.001%[14], listed in the Ge-68/Ga-68 generator specifications is perhaps most useful in the context of tracking generator performance, rather than for the evaluation of hazard to the patient associated with Ge-68 breakthrough. While it is true, of course, that Ge-68 breakthrough amounts exceeding the limit would contribute a higher radiation dose to the patient than those lower than the specified limit, the foregoing estimation of that dose makes it clear that even breakthrough at a relatively large excess above the limit would be inconsequential in terms of a possible adverse health effect on the patient. Further, even in the presence of Ge-68 in the eluate in amounts exceeding the breakthrough limit, higher activities of Ge-68 in the Ga-68 radiopharmaceutical preparation itself would likely not result. The aliquot of the Ga-68 eluate that is used for breakthrough determination is obtained prior to the generator elution passing through the protective guard column and is thereby collected in a manner which yields a breakthrough result which actually reflects the current performance. However, the guard column through which the eluate passes reduces the amount of Ge-68 present by 80% and thus the actual amount of Ge-68 administered to the patient as a radiocontaminant in a Ga-68 radiopharmaceutical would be far less than the measured Ge-68 breakthrough would suggest.

Changes to Guidance Considered by the Sub-committee and its Recommendations

General Comments

Title

No change is recommended.

Table of Contents

The Table of Contents should be revised to be consistent with the changes recommended in the Specific Comments below.

Purpose

No explicit purpose of the Guidance is specified as such (i.e., as the "Purpose"). It is 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). Inclusion of an explicit statement such as the following would be particularly helpful, "This Guidance provides applicants with an acceptable means of satisfying the requirements for a license for the use of a

[14] GalliaPharm Pharmaceutical GMP Grade $^{68}Ge/^{68}Ga$-Generator: Instructions for Use, Revision 1.4, Eckert & Ziegler Radiopharma GmbH, Berlin, Germany, May 27, 2016.

column based Ge-68/Ga-68 generator for producing Ga-68 to be used in the preparation of Ga-68 radiopharmaceuticals."

10 CFR 35.200 versus 10 CFR 35.1000 Use of Ge-68/Ga-68 Generators

The most problematic aspect of the Licensing Guidance, in the opinion of the ACMUI Sub-committee, is related to clarifying in the guidance that the regulation of Ge-68/Ga-68 generators used for production of Ga-68 radiopharmaceuticals is under 10 CFR 35.1000 and that the medical use of the Ga-68 radiopharmaceuticals remains under 10 CFR 35.200. Specifically, the Sub-committee is concerned that the scope of the current Licensing Guidance, which appears to be restricted to Section 35.200 and 35.1000 licensees, is too narrow because it does not explicitly apply to commercial nuclear pharmacies, since such entities are regulated under Part 32 (specifically CFR 32.72) rather than Part 35. The Sub-committee therefore recommends clarification of what, exactly, is regulated under 10 CFR 35.200 and 10 CFR 35.1000, respectively. It is only the Ge-68/Ga-68 generators, it appears, which are regulated under 10 CFR 35.1000, while Ga-68 radiopharmaceuticals are regulated under 10 CFR 35.200. It should therefore be stated that regulation of Ga-68 radiopharmaceuticals under 10 CFR 35.200 applies to patient dosages obtained from appropriately trained authorized users (AUs) or authorized nuclear pharmacists (ANPs) within a medical facility as well as from commercial nuclear pharmacies. Accordingly, the Sub-committee recommends revision of the passage in lines 73-84 on page 2 of the Licensing Guidance, including the section entitled, "Commercial Nuclear Pharmacy Use 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.

The foregoing recommendations thus generalize and clarify the Licensing Guidance, making it applicable both to commercial nuclear pharmacies and to medical facilities. Ga-68 can be used to radiolabel a wide variety of antibodies and antibody fragments as well as peptides and thus provide broadly applicable PET radiopharmaceuticals. The potential impact of the Ge-68/Ga-68 generator on molecular imaging is therefore significant and would potentially be delayed and otherwise undermined without these clarifications.

Specific Comments

Pg 2 Lines 54-61 This passage should be revised as follows.

> **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.

Pg 2 Line 69 The word, “present,” should be changed to, “specified.”

Pg 2 Lines 69-70 The phrase, “…, the use of Ga-68 eluted from a Ge-68 generator…,” should be changed to, “…the use of a Ge-68 generator…”

Pg 3 Lines 96 The word, “applicable,” should be inserted between the words, “the” and “general.”

Pg 3 Lines 98-111 This entire section, entitled, “General,” has been re-located to the section now entitled, “Use of Ga-68 Radiopharmaceuticals,” and therefore should be removed from this location in the Guidance. Note that the phrase, “Except for quantities that require a written directive under 10 CFR 35.40(b),…,” in Line 101 has been eliminated altogether, since Ga-68 will not be used therapeutically and therefore its use will not require a written directive.

Pg 4 Line 133 The term, "(ANPs)" should be changed to, "authorized nuclear pharmacists (ANPs)."

Pg 4 Line 142 The phrase, "…or an ANP," should be appended to the end of this line.

The statement, "Identify each ANP and provide documentation of their training and experience in accordance with 10 CFR 35.55," should be inserted as a separate paragraph immediately after Line 142.

Pg 4 Lines 144-145 This statement should be revised as follows, "Identify each AU and provide documentation of their training and experience in the use of Ge-68/Ga-68 generators for preparation of Ga-68 radiopharmaceuticals for imaging and localization studies.

Pg 4 Lines 147-148 This statement should be revised as follows, "The physician should be considered qualified for use of the Ge-68/Ga-68 generators to prepare Ga-68 radiopharmaceuticals if the licensee demonstrates that the individual meets the following."

Pp 4-5 Lines 156-204 This passage should be revised as follows.

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.

Note that the foregoing revision elimination the enumeration of the actual training and experience requirements originally included in the Licensing Guidance. Even in the unlikely event that a medical facility only used Ga-68 radiopharmaceuticals, explicitly referencing the training and experience requirements pursuant to 35.200 would be unambiguous.

Pg 5 Lines 208-209 This passage should be revised as follows.

> **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.

Pg 5 Lines 211-214 No breakthrough limit for Ge-68/Ga-68 generators has been specified in 10 CFR 35.204, so what constitutes "appropriate" breakthrough levels remains unspecified. If these are the limits specified by the generator manufacturer (as stated subsequently in the Guidance), that should be stated here as well.

Pg 6 Line 229 The phrase, "…are used for patients…," should be changed to, "…are to be used for patients…"

Pg 6 Line 243 What, exactly, is meant by "locations" - different institutions, different building within the same institutions, different rooms within the same building, or different areas in the same room?

Pg 7 Lines 279-280 This sentence should be revised as follows, "Survey all areas of licensed material use, including the generator storage and kit preparation areas, for contamination using a survey instrument each day of use."

Pg 7 Lines 280-282 The Guidance should include instructions/recommendations in the event that surveys of the Ge-68/Ga-68 generator indicate that it is leaking.

Pg 7 Lines 285-291 This passage should be revised as follows.

> 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:

Pg 7	Lines 293-295	This passage should be revised as follows, "2. the revision is based upon NRC's current guidance for use a Ge-68/Ga-68 generator under 35.1000 posted on the NRC Medical Uses Licensee Toolkit;…"
Pg 8	Lines 311-313	This passage should be revised as follows. Assay each patient dosage in the dose calibrator (or instrument) before administering it (10 CFR 35.63).
Pg 8	Line 316	The phrase, "…small activity of Ge-68…," should be changed to, "…a small amount of Ge-68 activity…"
Pg 8	Lines 343-344	This commitment on the part of the Applicant will require a fuller explanation once the NRC has finalized this exemption and all of the applicable conditions.
Pg 9	Line 361	The term, "authorization 8", refers to the information in the table in line 118 on page 3. That table should be specifically referenced and use the term, "Authorization 8".

Respectfully submitted, August 25 2016,
Sub-Committee on Germanium-68/Gallium-68 Generator Licensing Guidance,
Advisory Committee on the Medical Use of Isotopes (ACMUI),
Nuclear Regulatory Commission (NRC)

The ACMUI unanimously approved this report during its public teleconference meeting on August 10, 2016.

Appendix: Cited Sections of 10 CFR 32 and 35

§ 32.72 Manufacture, preparation, or transfer for commercial distribution of radioactive drugs containing byproduct material for medical use under part 35

(a) An application for a specific license to manufacture, prepare, or transfer for commercial distribution radioactive drugs containing byproduct material for use by persons authorized pursuant to part 35 of this chapter will be approved if:

(1) The applicant satisfies the general requirements specified in 10 CFR 30.33;

(2) The applicant submits evidence that the applicant is at least one of the following:

(i) Registered with the U.S. Food and Drug Administration (FDA) as the owner or operator of a drug establishment that engages in the manufacture, preparation, propagation, compounding, or processing of a drug under 21 CFR 207.20(a);

(ii) Registered or licensed with a state agency as a drug manufacturer;

(iii) Licensed as a pharmacy by a State Board of Pharmacy;

(iv) Operating as a nuclear pharmacy within a Federal medical institution; or

(v) A Positron Emission Tomography (PET) drug production facility registered with a State agency.

(3) The applicant submits information on the radionuclide; the chemical and physical form; the maximum activity per vial, syringe, generator, or other container of the radioactive drug; and the shielding provided by the packaging to show it is appropriate for the safe handling and storage of the radioactive drugs by medical use licensees; and

(4) The applicant satisfies the following labeling requirements:

(i) A label is affixed to each transport radiation shield, whether it is constructed of lead, glass, plastic, or other material, of a radioactive drug to be transferred for commercial distribution. The label must include the radiation symbol and the words "CAUTION, RADIOACTIVE MATERIAL" or "DANGER, RADIOACTIVE MATERIAL"; the name of the radioactive drug or its abbreviation; and the quantity of radioactivity at a specified date and time. For radioactive drugs with a half life greater than 100 days, the time may be omitted.

(ii) A label is affixed to each syringe, vial, or other container used to hold a radioactive drug to be transferred for commercial distribution. The label must include the radiation symbol and the words "CAUTION, RADIOACTIVE MATERIAL" or "DANGER, RADIOACTIVE MATERIAL" and an identifier that ensures that the syringe, vial, or other container can be correlated with the information on the transport radiation shield label.

(b) A licensee described by paragraph (a)(2)(iii) or (iv) of this section:

(1) May prepare radioactive drugs for medical use, as defined in 10 CFR 35.2, provided that the radioactive drug is prepared by either an authorized nuclear pharmacist, as specified in paragraph (b)(2) and (b)(4) of this section, or an individual under the supervision of an authorized nuclear pharmacist as specified in 10 CFR 35.27.

(2) May allow a pharmacist to work as an authorized nuclear pharmacist if:

(i) This individual qualifies as an authorized nuclear pharmacist as defined in 10 CFR 35.2,

(ii) This individual meets the requirements specified in § 35.55(b) and 35.59 of this chapter, and the licensee has received an approved license amendment identifying this individual as an authorized nuclear pharmacist; or

(iii) This individual is designated as an authorized nuclear pharmacist in accordance with paragraph (b)(4) of this section.

(3) The actions authorized in paragraphs (b)(1) and (b)(2) of this section are permitted in spite of more restrictive language in license conditions.

(4) May designate a pharmacist (as defined in § 35.2 of this chapter) as an authorized nuclear pharmacist if:

(i) The individual was a nuclear pharmacist preparing only radioactive drugs containing accelerator-produced radioactive material, and

(ii) The individual practiced at a pharmacy at a Government agency or Federally recognized Indian Tribe before November 30, 2007 or at all other pharmacies before August 8, 2009, or an earlier date as noticed by the NRC.

(5) Shall provide to the Commission:

(i) A copy of each individual's certification by a specialty board whose certification process has been recognized by the Commission or an Agreement State as specified in § 35.55(a) of this chapter with the written attestation signed by a preceptor as required by § 35.55(b)(2) of this chapter; or

(ii) The Commission or Agreement State license, or

(iii) Commission master materials licensee permit, or

(iv) The permit issued by a licensee or Commission master materials permittee of broad scope or the authorization from a commercial nuclear pharmacy authorized to list its own authorized nuclear pharmacist, or

(v) Documentation that only accelerator-produced radioactive materials were used in the practice of nuclear pharmacy at a Government agency or Federally recognized Indian Tribe before November

30, 2007 or at all other locations of use before August 8, 2009, or an earlier date as noticed by the NRC; and

(vi) A copy of the State pharmacy licensure or registration, no later than 30 days after the date that the licensee allows, under paragraphs (b)(2)(i) and (b)(2)(iii) of this section, the individual to work as an authorized nuclear pharmacist.

(c) A licensee shall possess and use instrumentation to measure the radioactivity of radioactive drugs. The licensee shall have procedures for use of the instrumentation. The licensee shall measure, by direct measurement or by combination of measurements and calculations, the amount of radioactivity in dosages of alpha-, beta-, or photon-emitting radioactive drugs prior to transfer for commercial distribution. In addition, the licensee shall:

(1) Perform tests before initial use, periodically, and following repair, on each instrument for accuracy, linearity, and geometry dependence, as appropriate for the use of the instrument; and make adjustments when necessary; and

(2) Check each instrument for constancy and proper operation at the beginning of each day of use.

(d) Nothing in this section relieves the licensee from complying with applicable FDA, other Federal, and State requirements governing radioactive drugs.

[59 FR 61780, Dec. 2, 1994; 59 FR 65244, Dec. 19, 1994, as amended at 60 FR 324, Jan. 4, 1995; 67 FR 20370, Apr. 24, 2002; 67 FR 62872, Oct. 9, 2002; 67 FR 77652, Dec. 19, 2002; 71 FR 15007, Mar. 27, 2006; 72 FR 45150, Aug. 13, 2007; 72 FR 55929 Oct. 1, 2007; 77 FR 43695, Jul. 25, 2012]

§ 35.12 Application for license, amendment, or renewal.

(a) An application must be signed by the applicant's or licensee's management.

(b) An application for a license for medical use of byproduct material as described in §§ 35.100, 35.200, 35.300, 35.400, 35.500, 35.600, and 35.1000 must be made by--

(1) Filing an original and one copy of NRC Form 313, "Application for Material License," that includes the facility diagram, equipment, and training and experience qualifications of the Radiation Safety Officer, authorized user(s), authorized medical physicist(s), and authorized nuclear pharmacist(s); and

(2) Submitting procedures required by §§ 35.610, 35.642, 35.643, and 35.645, as applicable.

(c) A request for a license amendment or renewal must be made by--

(1) Submitting an original and one copy of either--

(i) NRC Form 313, "Application for Material License"; or

(ii) A letter requesting the amendment or renewal; and

(2) Submitting procedures required by §§ 35.610, 35.642, 35.643, and 35.645, as applicable.

(d) In addition to the requirements in paragraphs (b) and (c) of this section, an application for a license or amendment for medical use of byproduct material as described in § 35.1000 must also include information regarding any radiation safety aspects of the medical use of the material that is not addressed in Subparts A through C of this part.

(1) The applicant shall also provide specific information on--

(i) Radiation safety precautions and instructions;

(ii) Methodology for measurement of dosages or doses to be administered to patients or human research subjects; and

(iii) Calibration, maintenance, and repair of instruments and equipment necessary for radiation safety.

(2) The applicant or licensee shall also provide any other information requested by the Commission in its review of the application.

(e) An applicant that satisfies the requirements specified in § 33.13 of this chapter may apply for a Type A specific license of broad scope.

[67 FR 20370, Apr. 24, 2002; 67 FR 62872, Oct. 9, 2002]

§ 35.63 Determination of dosages of unsealed byproduct material for medical use.

(a) A licensee shall determine and record the activity of each dosage before medical use.

(b) For a unit dosage, this determination must be made by—

(1) Direct measurement of radioactivity; or

(2) A decay correction, based on the activity or activity concentration determined by—

(i) A manufacturer or preparer licensed under § 32.72 of this chapter or equivalent Agreement State requirements; or

(ii) An NRC or Agreement State licensee for use in research in accordance with a Radioactive Drug Research Committee-approved protocol or an Investigational New Drug (IND) protocol accepted by FDA; or

(iii) A PET radioactive drug producer licensed under § 30.32(j) of this chapter or equivalent Agreement State requirements.

(c) For other than unit dosages, this determination must be made by—

(1) Direct measurement of radioactivity;

(2) Combination of measurement of radioactivity and mathematical calculations; or

(3) Combination of volumetric measurements and mathematical calculations, based on the measurement made by:

(i) A manufacturer or preparer licensed under § 32.72 of this chapter or equivalent Agreement State requirements; or

(ii) A PET radioactive drug producer licensed under § 30.32(j) of this chapter or equivalent Agreement State requirements.

(d) Unless otherwise directed by the authorized user, a licensee may not use a dosage if the dosage does not fall within the prescribed dosage range or if the dosage differs from the prescribed dosage by more than 20 percent.

(e) A licensee shall retain a record of the dosage determination required by this section in accordance with § 35.2063.

[72 FR 55931, Oct. 1, 2007]

§ 35.200 Use of unsealed byproduct material for imaging and localization studies for which a written directive is not required.

Except for quantities that require a written directive under § 35.40(b), a licensee may use any unsealed byproduct material prepared for medical use for imaging and localization studies that is—

(a) Obtained from:

(1) A manufacturer or preparer licensed under § 32.72 of this chapter or equivalent Agreement State requirements; or

(2) A PET radioactive drug producer licensed under § 30.32(j) of this chapter or equivalent Agreement State requirements; or

(b) Excluding production of PET radionuclides, prepared by:

(1) An authorized nuclear pharmacist;

(2) A physician who is an authorized user and who meets the requirements specified in § 35.290, or 35.390 and 35.290(c)(1)(ii)(G); or

(3) An individual under the supervision, as specified in § 35.27, of the authorized nuclear pharmacist in paragraph (b)(1) of this section or the physician who is an authorized user in paragraph (b)(2) of this section;

(c) Obtained from and prepared by an NRC or Agreement State licensee for use in research in accordance with a Radioactive Drug Research Committee-approved protocol or an Investigational New Drug (IND) protocol accepted by FDA; or

(d) Prepared by the licensee for use in research in accordance with a Radioactive Drug Research Committee-approved application or an Investigational New Drug (IND) protocol accepted by FDA.

[67 FR 20370, Apr. 24, 2002, as amended at 68 FR 19324, Apr. 21, 2003; 69 FR 55738, Sep. 16, 2004; 70 FR 16363, Mar. 30, 2005; 71 FR 15009, Mar. 27, 2006; 72 FR 55932 Oct. 1, 2007]

§ 35.290 Training for imaging and localization studies.

Except as provided in § 35.57, the licensee shall require an authorized user of unsealed byproduct material for the uses authorized under § 35.200 to be a physician who—

(a) Is certified by a medical specialty board whose certification process has been recognized by the Commission or an Agreement State and who meets the requirements in paragraph (c)(2) of this section. (The names of board certifications which have been recognized by the Commission or an Agreement State will be posted on the NRC's Web page.) To have its certification process recognized, a specialty board shall require all candidates for certification to:

(1) Complete 700 hours of training and experience in basic radionuclide handling techniques and radiation safety applicable to the medical use of unsealed byproduct material for imaging and localization studies as described in paragraphs (c)(1)(i) through (c)(1)(ii)(G) of this section; and

(2) Pass an examination, administered by diplomates of the specialty board, which assesses knowledge and competence in radiation safety, radionuclide handling, and quality control; or

(b) Is an authorized user under § 35.390 and meets the requirements in § 35.290(c)(1)(ii)(G), or equivalent Agreement State requirements; or

(c)(1) 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 authorized user who meets the requirements in §§ 35.57, 35.290, or 35.390 and 35.290(c)(1)(ii)(G), or equivalent Agreement State requirements, 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

(2) Has obtained written attestation, signed by a preceptor authorized user who meets the requirements in §§ 35.57, 35.290, or 35.390 and 35.290(c)(1)(ii)(G), or equivalent Agreement State requirements, that the individual has satisfactorily completed the requirements in paragraph (a)(1) or (c)(1) of this section and has achieved a level of competency sufficient to function independently as an authorized user for the medical uses authorized under §§ 35.100 and 35.200.

[67 FR 20370, Apr. 24, 2002, as amended at 68 FR 19324, Apr. 21, 2003; 69 FR 55738, Sep. 16, 2004; 70 FR 16364, Mar. 30, 2005; 71 FR 15009, Mar. 27, 2006; 72 FR 45151, Aug. 13, 2007; 74 FR 33905, Jul. 14, 2009]

§ 35.1000 Other medical uses of byproduct material or radiation from byproduct material.

A licensee may use byproduct material or a radiation source approved for medical use which is not specifically addressed in subparts D through H of this part if--

(a) The applicant or licensee has submitted the information required by § 35.12(b) through (d); and

(b) The applicant or licensee has received written approval from the Commission in a license or license amendment and uses the material in accordance with the regulations and specific conditions the Commission considers necessary for the medical use of the material.