Advisory Committee on the Medical Use of Isotopes (ACMUI)

Germanium-68 (Ge-68) Decommissioning Funding Plan (DFP) Final Report

August 12, 2015

Subcommittee Members: F. Costello; S. Langhorst; S. Mattmuller (Chair); C. Palestro; and P. Zanzonico

Challenge: The restrictive aspects of a decommissioning funding plan (DFP) for Ge-68 that arise from the current Part 30 regulations are preventing and/or deterring the use of promising Gallium-68 (Ga-68) diagnostic imaging agents for patients.

Charge:

1) **Estimate the number of potential Ge/Ga-68 generator licenses affected, and**
2) **Recommend to the Committee on which route of action it believes NRC should pursue to address the decommissioning funding plan issue.**

Background: Neuroendocrine tumor imaging (NET), why Ge-68 is so important to NET patients.

Neuroendocrine tumors (NET) present a difficult diagnostic challenge. For NET patients, it currently takes on average seven years for a proper diagnosis to be made and appropriate therapy prescribed. Fortunately, diagnostic imaging of patients with NET is on the verge of making dramatic advancements in this area.

There is a new class of radiopharmaceuticals using a positron emitter radionuclide, Ga-68, that are nearing FDA approval. The Ga-68 is attached to one of several somatostatin receptor (SSR) binding peptides via the DOTA chelator, that is, DOTA-TATE, DOTA-TOC, and DOTA-NOC, (DOTAs). The advantages of these new radiopharmaceticals can be best demonstrated by a comparison of their images in the same patient (Figure 1).

In the left two panels are images produced with In-111 DTPA-Octreotide (In-111 Octreotide), the current SSR radiopharmaceutical in routine clinical use today. In the right panel is a positron emission tomography (PET) image produced with the Ga-68 DOTA-TOC.

The advantages of the Ga-68 imaging are readily apparent. This PET image leads to greater sensitivity and specificity resulting in superior accuracy for this diagnostic imaging procedure. There is also greater patient convenience as the Ga-68 DOTA image only takes one day versus two days needed for the In-111 Octreotide image. For a patient who has to travel several hours for this procedure, this shorter time can save them from a potential overnight stay. Finally, the radiation dosimetry burden to the patient is less for the Ga-68 DOTAs image versus the In-111 Octreotide image, with a nearly a five-fold reduction in the effective dose to the patient (2.3 and 10.8 mSv, respectively, for Ga-68 and In-111).

Importantly, the source of Ga-68 is a generator, rather than a cyclotron. As a result, the availability and clinical utility is potentially far greater than those of current-generation PET isotopes. Ga-68 is continuously produced in this generator by the decay of its parent radionuclide Ge-68. Additional information regarding the Ga-68 generator is presented below in the section on the design and operation of a Ge-68 generator.

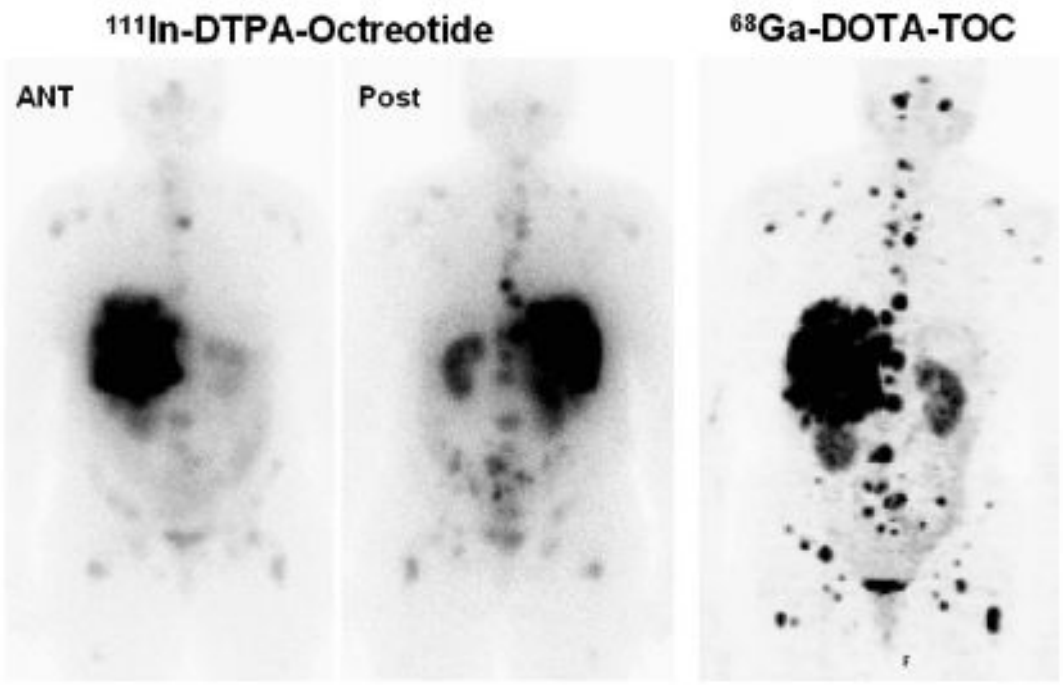

Figure 1

Background: Regulatory DFP trigger for a Ga-68 generator

The regulations requiring licensees to submit decommissioning funding plans (10 CFR 30.35) became effective on July 27, 1988. The trigger level (i.e., a quantity of a given radionuclide) for a DFP comes from a calculation using a labeling quantity for a radionuclide listed in the appendix entitled, "Quantities of Licensed Material Requiring Labeling." The calculation involves multiplying the labeling quantity by 10^5 to derive the trigger level. At this time, however, Ge-68 is not listed on the table, so a very small default quantity of only 10 mCi (0.1 uCi x 10^5) is derived as the trigger level. Initially, this was not problematic as Ge-68 was not regulated by the NRC.

Prior to 2007, a site with a Ga-68 generator did not need a DFP since the NRC did not yet have the authority to regulate it. The NRC's regulatory authority for Ge-68 came into effect in 2007, with the adoption of an expanded definition of by-product material to include accelerator-produced radionuclides

Despite now having authority over these additional radionuclides, the NRC did not amend Appendix B to Part 30 at that time. Appendix B continues to have no listing for Ge-68 and the same calculated 10 mCi trigger level exists as first established in 1988. This 27-year-old 10-mCi trigger level persists and a DFP is thus required for the use of a new Ga-68 generator.

Impact of DFPs on medical licensees

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 Ga-68 generator is used but also all areas where radioactive materials are used under the same license.

Consider the example of a mid-size medical center and the various areas of use its license may include:

- Nuclear Medicine facility, including SPECT imaging rooms and a radiopharmacy for the preparation of radiopharmaceuticals;
- PET imaging rooms;
- Multiple satellite cardiac imaging suites throughout the surrounding area;
- Radiation Oncology, including gamma knife and brachytherapy;
- Affiliated hospital with its own Nuclear Medicine facility, including SPECT imaging rooms and a radiopharmacy

Without a Ga-68 generator, a DFP is very likely not needed for such a medical center. However, if such a center were to add a Ga-68 generator, it would have to develop a DFP and not just for the one room that would house the generator, but for all of the foregoing areas. A DFP thus becomes very extensive and very expensive, perhaps prohibitively so for a licensee with numerous areas of use.

This scenario did, in fact occur last year at a large university-based medical center on the East Coast. This center attempted to acquire a Ga-68 generator for clinical investigation, but their DFP was very extensive because of all of their areas of use and would have been very expensive to fund. Hence they did not acquire the necessary financial assurances for a DFP and were restricted to acquiring a used Ga-68 generator of less than 10 mCi in activity. The center was not able to conduct their research in patients as initially planned and was only able to perform research in small animals. It was their radiation safety officer who was the first to succinctly and accurately describe a DFP as “extensive and expensive.” It was extensive as over 170 man-hours were required from the radiation safety office alone to prepare the DFP. This total does not include the large number of man-hours needed from numerous other departments for the preparation of the DFP. It was expensive, as the financial assurances in the form of a bond would need to be purchased to cover the decommissioning expenses of over one million dollars. This expense continues on an annual basis.

The restrictive aspects arising from the current Part 30 regulations are preventing and/or deterring the use of promising Gallium-68 (Ga-68) diagnostic imaging agents for patients due to the decommissioning funding plan burden for its parent Ge-68.

Charge 1: Estimate the number of potential Ge-68/Ga-68 generator licenses affected.

At first glance, this appears to be a reasonable request, one that could be addressed by sending survey-type questionnaires to a sample of licensees so as to extrapolate to a number of licensees nationally. However, given how extensive of an effort it is to prepare a DFP, this actually is a very complex and time consuming effort for each licensee (as illustrated for the licensee discussed above). A DFP is unique to each licensee, and once prepared it is only applicable to that licensee and cannot be used by another licensee. Neither the licensees nor the subcommittee have the time or other resources to conduct and answer such a survey. Most likely the NRC does not either and it is therefore impractical to collect firm numbers on licensees affected.

There are other ways we can estimate the effect of the extensive and expensive components of a DFP on the availability of the Ga-68 DOTAs. As we do know, it has already deterred the use of Ga-68 DOTAs in patients. For example in the case of the DFP on the university-based East Coast medical center discussed above, the impact was to effectively prevent the clinical use of Ga-68 radiopharmaceuticals. It has also been known to deter the use of Ga-68 DOTA radiopharmaceuticals elsewhere.[1]

> "Currently in the US there are only three active sites that are reliably imaging patients with the Ga-68 DOTA radiopharmaceuticals. These sites include the National Institute of Health, Stanford University and the University of California in San Francisco. Three sites total within all of the United States. The current wait for a NET patient is over 2+ months at the NIH."

[1] Personal communication with Josh Mailman, President of the NorCal CarciNet Community, a patient advocacy group for neuroendocrine tumor patients. https://norcalcarcinet.org/

Although the subcommittee cannot project the future impact of the DFP requirement on future of Ga-68 DOTAs, the statement was submitted by one of the largest commercial radiopharmacy companies in the US, Triad Isotopes[2]:

> Triad Isotopes, a leading commercial provider of radiopharmaceuticals, operates over 50 nuclear pharmacies in markets throughout the United States.
>
> Under the current regulations, the complexity and cost of a DFP would potentially hinder our ability to provide Ga-68 radiopharmaceuticals from our nuclear pharmacies to all areas of the country. The net effect is that the DFP regulations would likely limit the availability of this radiopharmaceutical, for several reasons:
>
> - First, economic pressures will impede adoption. The difficulty to compensate for the fixed costs of the DFP will limit the number of radiopharmacies that will be able to offer Ga-68 radiopharmaceuticals.
> - Second, the short half-life of Ga-68 will make this a challenging radiopharmaceutical to distribute. To ensure good usage across the country, the product will need to be available through as many nuclear pharmacies as possible; however, it would be difficult to dispense and deliver through a long spoke-hub model due to that short half-life of 68 minutes.
> - Taking both cost and distribution challenges into account, it is unlikely that nuclear pharmacy networks such as ours would provide Ga-68 related radiopharmaceuticals to all areas of the country if a DFP was initiated; thus, every patient in need would not have equal access to these radiopharmaceuticals, most especially those in smaller and/or more rural markets.

This statement from Triad has added weight in that at four of their sites they do have a DFP in place; hence, they are well aware of how extensive and expensive a DFP can be. Patient access is already clearly hindered in the U.S. by the small number of licensees who can provide Ga-68 DOTAs. Regulatory relief from the DFP is urgently needed to increase patient access to these invaluable radiopharmaceuticals.

[2] Personal communication with Fred Gattas, Director, Quality Control and Safety, Triad Isotopes

Charge 2: Recommend to the Committee on which route of action it believes NRC should pursue to address the decommissioning funding plan issue.

The subcommittee recommends the following language be added as a footnote to Appendix B Part 30 -- Quantities[1] of Licensed Material Requiring Labeling as the most expeditious, cost effective, and practical route to addressing the DFP issues.

> [3]This does not include Ge-68 in a Ge-68/Ga-68 medical use generators (limit less than 10^5 x 2 uCi) that are returned to the manufacturer at end of use.

(Note: Given the title of Appendix B -- Quantities of Licensed Material Requiring Labeling the 2 uCi will be considered a new "labeling" quantity for Ge-68)

This new calculated limit of 200 mCi as a trigger amount for a DFP would only be allowed for Ge-68 in a Ga-68 generator for medical use. This limit would allow for the use of a Ga-68 generator for clinical use and at the end of its one-year shelf-life allow it to be used for research such as in small animals. Regardless of its use, when the licensee is finished using the Ga-68 generator, it would be returned to the manufacturer for final disposal. The new limit would also allow a licensee to possess more than one generator to maintain a higher useful amount of Ga-68 available at all times for the preparation of Ga-68 DOTAs.

In order to maintain a higher useful amount of Ga-68, a licensee may purchase several Ga-68 generators with staggered calibration dates. This would be done much in the same way a radiopharmacy currently maintains a higher useful amount of Tc-99m with the purchase of Tc-99m generators with staggered calibrations dates, the difference being a staggered time interval of only 2-3 days for Tc-99m generators versus ~ 6 months for Ga-68 generators. For example, a licensee who also performs research may have the following Ga-68 generators on-hand if they purchase a new one every six months (Table 1).

Table 1: Activity of Ga-68 Generators -- Use is for both clinical and research

Age	Decay Factor	mCi of Ge-68
new	1	50.0
6 mos	0.63	31.5
12 mos	0.39	19.5
+new	1	50.0
18 mos[1]	0.24	12.2
24 mos[1]	0.15	7.6
Total		170.8

[1] These generators would only be used for research

The three major factors that we believe serve as the basis for this recommendation for this new labeling quantity of Ge-68 are as follow.

1. Under normal operation, the Ge-68 is stably bound within the generator. The design and operation of the Ga-68 generator thus ensures that it will have nearly the same safety profile as a sealed source device.

2. At the end of its use, the generator is returned to the manufacturer for final disposal. This disposal step in essence eliminates any concern at a licensee regarding Ge-68 associated DFP.

3. If Appendix B were to be revised, it would be appropriate to add Ge-68 with a labeling quantity of 10 uCi. *However, the subcommittee currently recommends a more conservative number of only 2 uCi for the purposes of a Direct Final Rulemaking.*

Design and Operation of the Ga-68 Generator

The Ga-68 generator is a device that serves as source of this important radionuclide. Ga-68 decays by positron emission and thus can be used for called positron emission tomography (PET) diagnostic medical imaging procedures. The vast majority of radionuclides used for PET imaging require a large and expensive particle accelerator such as a cyclotron. One of the best advantages of the Ga-68 generator, therefore, is that it provides a PET radionuclide without a cyclotron.

Currently, Ga-68 is used mainly in the preparation of the Ga-68 DOTAs, which have already emerged as the radiopharmaceutical of choice for NETs. The advantages of the Ga-68 DOTAs will greatly enhance the diagnosis and treatment of NET patients across the country.

In this generator Ge-68 is the parent radionuclide and it has a half-life of 271 days. It decays by electron capture to its daughter radionuclide, Ga-68, which has a half-life of 68 minutes. The generator is a closed system device consisting of a column containing a resin on which the parent radionuclide Ge-is fixed. Ga-68 is continuously produced by the decay of its radioactive parent Ge-68. The Ga-68 is removed from the generator by eluting it off the column with a sterile hydrochloric acid solution. The Ga-68 is soluble in the hydrochloric solution and readily elutes off the column. The Ge-68 is insoluble in the hydrochloric solution and remains fixed on the column and continues to decay to provide additional Ga-68 in future elutions. The Ga-68 generator is a device whose sole purpose is to provide Ga-68. Chemically, the Ga-68 is in the form of gallium chloride ($GaCl_3$) and is used in the preparation of the Ga-68 DOTAs. The Ga-68 as eluted cannot be used directly in patients.

The physical characteristics of both the parent and daughter radionuclides are summarized in Table 2.

Table 2: Physical characteristics of Ge-68 and Ga-68

	Ge-68	Ga-68
Half-live	270.95 days	67.71 minutes
Type of decay	Electron capture	Positron emission
X-rays	9.225 keV (13.1 %) 9.252 keV (25.7 %) 10.26 keV (1.64 %) 10.264 keV (3.2 %) 10.366 keV (0.03 %)	8.616 keV (1.37 %) 8.639 keV (2.69 %) 9.57 keV (0.55 %)
gammas		511 keV (178.28 %), 578.55 keV (0.03 %) 805.83 keV (0.09 %), 1077.34 keV (3.22 %) 1260.97 keV (0.09 %) 1883.16 keV (0.14 %)
beta+		Energy max. Energy 352.60 keV 821.71 keV (1.20 %) 836.00 keV 1899.01 keV (87.94 %)
Data derived from nudat (www.nndc.bnl.gov)		

The Ge-68 is easy to shield as during its decay it has no particulate or penetrating (i.e. high-energy) photon emissions, but only has low energy X-ray emissions. Shielding is, of course, needed for the Ga-68 as it decays by positron emission, with the subsequent production of 511-keV annihilation gamma rays.

A schematic of a generic Ga-68 generator is provided in Figure 2. Note that it has one inlet for the hydrochloric acid eluent and one outlet for the collection of the Ga-68.

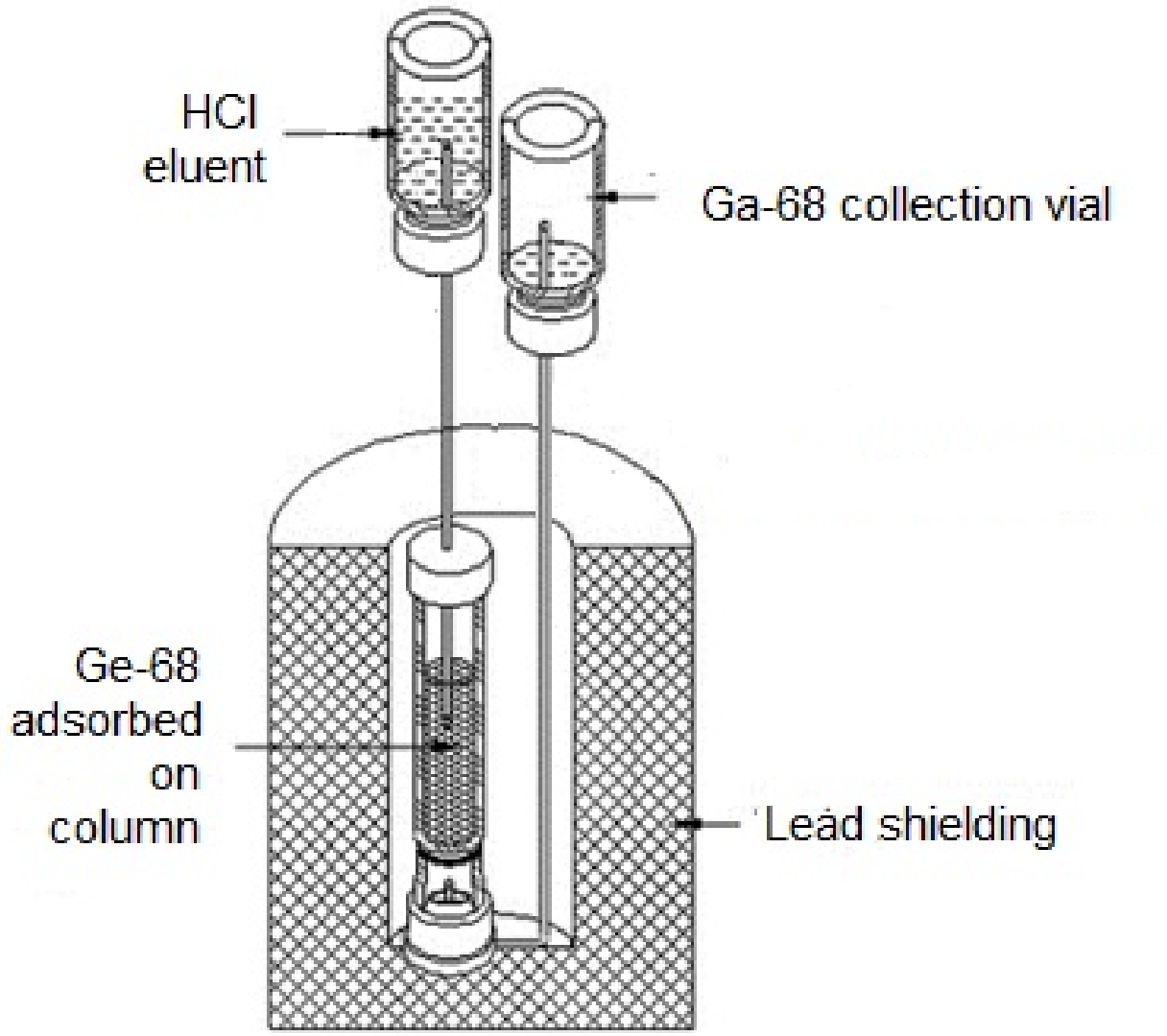

Figure 2.

It is a simple device that has no moving parts. The Ge-68, as a solid, is fixed onto the resin within the column by the chemical process of adsorption and thereby remains entirely within the generator and its heavy lead shielding.

The first Ga-68 generator manufactured in accordance with a Drug Master File for use in the United States is the Galliapharm by Eckert and Ziegler. It is a relatively small and compact device measuring 9 inches x 5.2 inches x 5.2 inches (H x W x D). It weighs approximately 31 pounds. See Figures 3-5. Again note the simplicity of the device, with only one inlet port and one outlet port and no moving parts.

Sectional view of the Galliapharm radionuclide generator

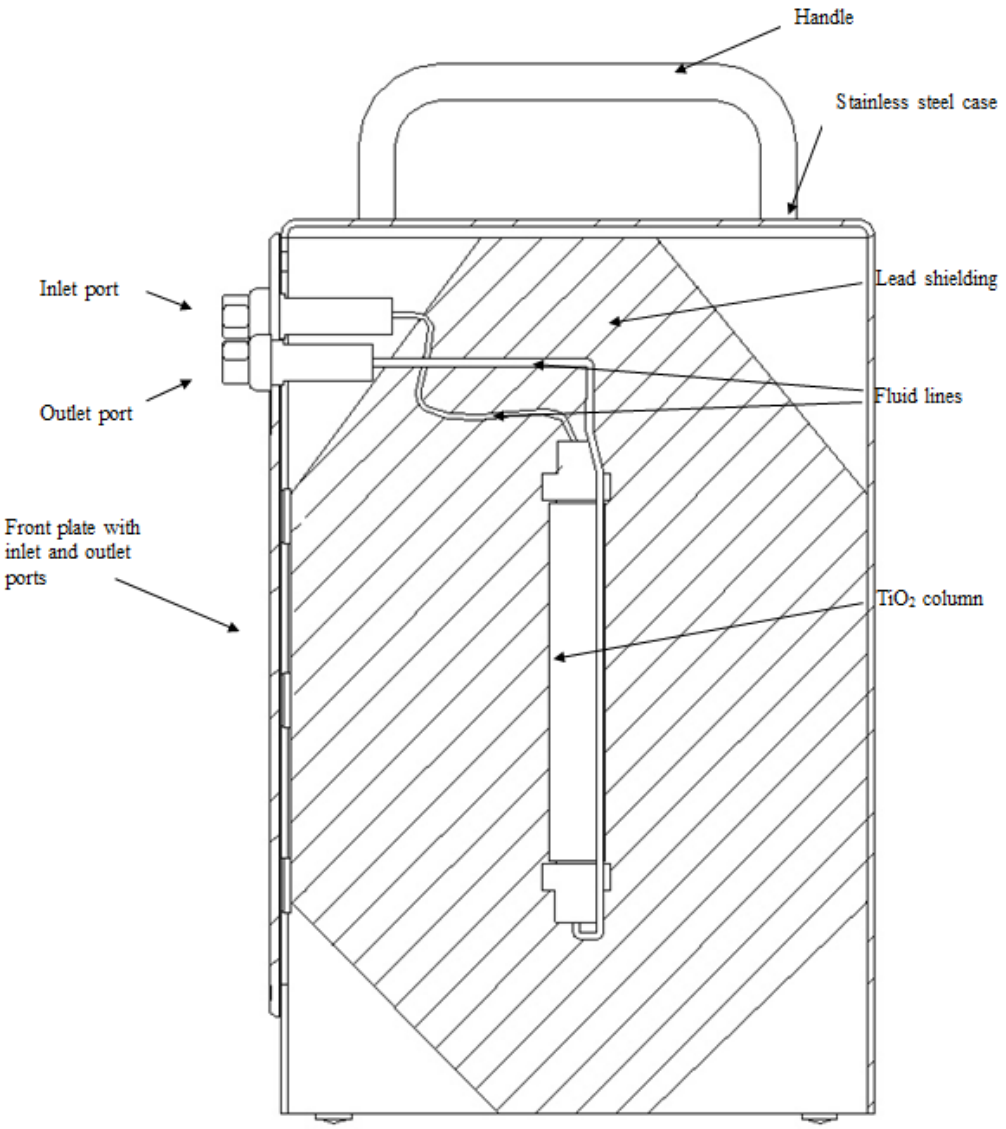

Figure 3.

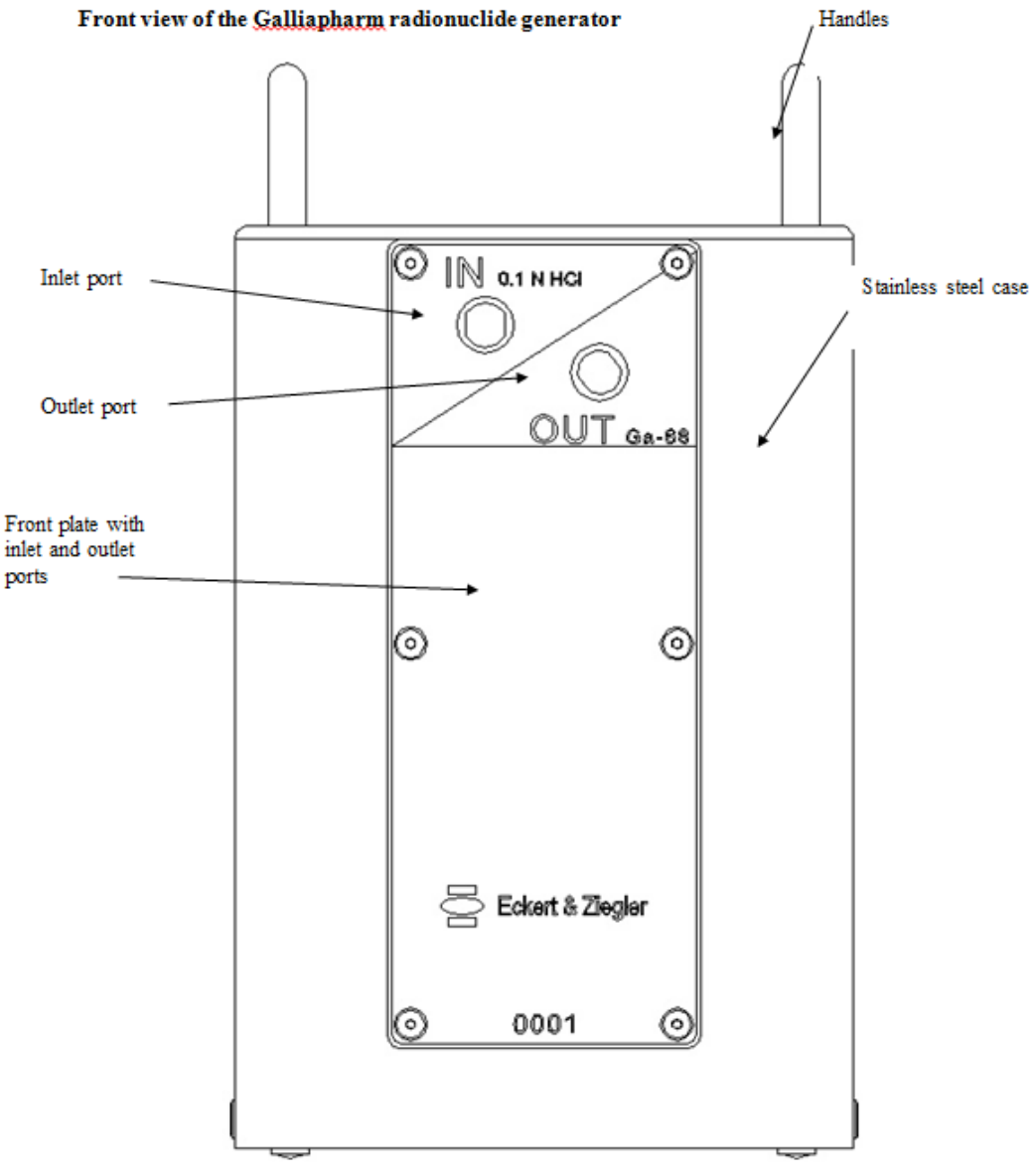

Figure 4.

Once the generator is placed in position in the nuclear medicine facility, it is not moved but simply remains in place for its entire lifetime. Due to its compact size, the generator and the associated chemistry module are typically placed together in the same hot cell. This close placement also has a chemistry advantage; by keeping the outlet line connecting the generator to the chemistry module as short as possible, the yields of the syntheses of the drug product are maximized.

The inlet line has a customized thread on its fitting to avoid a miss-connection; that is, it will only connect to the inlet port. Likewise, the outlet line will only connect to the outlet port. Because the generator remains in place once positioned, there are no mechanical stresses that could potentially lead to a leakage of activity.

Figure 5.

During the normal elution process of the Ga-68 generator, a very small amount of Ge-68 measured in nanocuries does get displaced from the column; this is known as parent breakthrough and is a phenomenon associated with all radionuclide generators. Ge-68 breakthrough is expressed as a percentage of total Ga-68 activity eluted from the column, corrected for decay. The specification for Ge-68 breakthrough is not more than 0.001% of the eluted Ga-68 activity. The breakthrough for this generator typically begins as low as 0.0001% when the generator is new and may rise slightly with the number of elutions. To minimize the breakthrough, it is recommended that the generator should be eluted at least once per working day. When used accordingly, the breakthrough should remain below the 0.001% limit for 12 months. The volume of the elution is ~ 5 mL, and the recommended rate of elution no greater than 2 mL/min. The breakthrough amounts are so low that unlike other medical use generators (i.e., Tc-99m or Rb-82 generators) the breakthrough cannot be measured with a dose calibrator. More sensitive equipment must be used to measure the amount of Ge-68 in a Ga-68 elution.

If an elution is not used for a Ga-68 radiopharmaceutical preparation, (i.e., was performed for maintenance of the column to minimize breakthrough), these unused elutions may be collected into a small waste vial and then stored for a day for decay (21 half-lives). For final disposal, since it is an acid solution it may need to be placed into a chemical waste container or, depending on a site's location one may be able to dispose of it in the sanitary sewer via a sink.

For example, for this latter scenario, with a breakthrough of 0.0001% when the generator is new and at its highest activity of 50 mCi the Ge-68 activity would only be a small amount of 0.03 µCi (or 30 nCi) of Ge-68 (= 50 mCi x 60% elution yield x 0.0001% breakthrough) per elution. The limits for disposal in sewerage are specified in § 20.2003 Disposal by release into sanitary sewerage and its associated Appendix B, see table 3.

Germanium-68

Atomic No.	Radionuclide	Class	Table 1 Occupational Values			Table 2 Effluent Concentrations		Table 3 Releases to Sewers
			Col. 1	Col. 2	Col. 3	Col. 1	Col. 2	
			Oral Ingestion ALI (µCi)	Inhalation		Air (µCi/ml)	Water (µCi/ml)	Monthly Average Concentration (µCi/ml)
				ALI (µCi)	DAC (µCi/ml)			
32	Germanium-68	D, see ^{66}Ge	5E+3	4E+3	2E-6	5E-9	6E-5	6E-4
		W, see ^{66}Ge	-	1E+2	4E-8	1E-10	-	-

Table 3.

This limit is calculated by dividing the amount of 0.03 µCi of Ge-68 by the concentration limit of 0.0006 µCi/mL (from the appendix), which equals 50 mL of required sewerage volume to meet the monthly average concentration.

In other words, less than two ounces (i.e., ¼ cup) of sewerage are needed for dilution for each elution disposed of to maintain the concentration of Ge-68 below the sewerage limits of § 20.2003. These conditions can easily be achieved if the elution is first held for one day for the decay of the Ga-68 and then disposed of in the sewerage.

Despite these nanocurie amounts of Ge-68 that come off the column with each elution, the Ga-68 generator could be considered for all practical purposes a sealed source device. As such it would be exempt from any DFP requirement pursuant to § 30.35 Financial assurance and recordkeeping for decommissioning.

While the small footprint and the simplistic ease of use of a Ga-68 generator are significant advantages over a cyclotron in producing a PET radionuclide it does have one limitation: the relatively small quantity of Ga-68 that it is able to produce compared, for example, to the output of a cyclotron. The relatively small output of a Ga-68 generator (i.e., mCi vs. Ci) and Ga-68's relatively short half-life will result in a radiopharmacy having a much smaller distribution area for Ga-68 radiopharmaceuticals than that for F-18 and/or Tc-99 radiopharmaceuticals. Therefore, there will be a need for a large number of radiopharmacies across the country to have the capability to prepare Ga-68 DOTA to provide equitable access for all patients nationwide.

Disposal of the Ga-68 Generator

Disposal by the licensee is very simple; at the end of its useful lifetime the generator is returned to the manufacturer for final disposal. Final disposal by the manufacturer in essence eliminates any concern regarding Ge-68 in regards to a DFP for the licensee. See, for example, the letter below from Eckert & Ziegler (Figure 6).

Eckert & Ziegler

Eckert & Ziegler Radiopharma GmbH, Robert-Rössle-Straße 10, D-13125 Berlin

TO WHOM IT MAY CONCERN

Eckert & Ziegler
Radiopharma GmbH

Robert-Rössle-Straße 10
D-13125 Berlin
www.ezag.de

Alina Hue
Sales & Customer Support

Telefon +49 (0)30 94184-280
Telefax +49 (0)30 94184-470
e-mail radiopharma@ezag.de

Berlin, 16.07.2015

Return ^{68}Ge / ^{68}Ga GalliaPharm generator

Herewith we, **Eckert & Ziegler Radiopharma GmbH**, located at Robert-Rössle-Str. 10, 13125 Berlin, Germany, confirm that we are obliged to keep back the used ^{68}Ge/^{68}Ga Pharmaceutical Grade Generator (GalliaPharm).

Additional service fees will apply, if you want E&Z to take care of the final disposal of the used product.

Best regards,

A. Hue

Eckert & Ziegler
Radiopharma GmbH
Robert-Rössle-Straße 10
13125 Berlin-Germany

Alina Hue
Sales & Customer Support

Figure 6.

Propriety of current default labeling quantity of 0.1 uCi for Ge-68

The subcommittee reviewed the radionuclides currently listed in Appendix B. Table 4 below contains all of the radionuclides from Appendix B that have a labeling quantity of 10 uCi and a half-life greater than 120 days in order to assess the impact of changing the labeling quantity for Ge-68 from 0.1 uCi to 2 uCi.

What is quite surprising from this review are the number of radionuclides with substantially longer half-lives than Ge-68 but with a labeling quantity that is 100x greater than the current value for Ge-68 of 0.1 uCi.

Licensed Material	Quantity (µCi)	Half-Life*	Decay Mode*
Sb-125	10	2.76 y	β-
Ba-133	10	10.6 y	EC
Ca-45	10	162.6 d	β-
Cs-135	10	2.3e6 y	β-
Cs-137	10	30.1 y	β-
Cl-36	10	3.01e5 y	EC+, β+, β-
Eu-155	10	4.75 y	β-
Gd-153	10	240 d	EC
Fe-55	10	2.74 y	EC
Mn-54	10	312 d	EC, β-
Ni-63	10	101 y	β-
Nb-93m	10	16.1 y	IT
Pr-147	10	2.62 y	β-
Rb-87	10	4.81e10 y	β-
Sm-151	10	90 y	β-
Tl-204	10	3.78 y	EC, β-
Tm-170	10	129 d	EC, β-
Tm-171	10	1.92 y	β-
Zn-65	10	244 d	EC+, β+

Licensed Material	Quantity (µCi)	Half-Life*	Decay Mode*
Zr-93	10	1.61e6 y	β-
Ge-68	0.1	217 d	EC

* http://www.nndc.bnl.gov/mird/

Table 4.

In the past 27 years, Appendix B has not been revised, and Ge-68 may not have been included initially as the NRC did not have regulatory authority over it. Subsequently, in 1992-1994, Appendix C but not Appendix B added a labeling quantity for Ge-68. This occurred even though the NRC still did not have authority over Ge-68. Unfortunately, when the NRC did gain authority over Ge-68 in 2007, a revision of Appendix B was deemed "beyond the scope" of that action and did not occur.

If a revision of Appendix B had ever taken place, it appears that Ge-68 would easily have been included among the group of radionuclides with a labeling quantity of 10 uCi. Our proposed labeling quantity of 2 uCi is thus conservative as it would still offer a five-fold "safety factor" versus a labeling quantity of 10 uCi, (i.e., a 200-mCi trigger limit versus a 1,000-mCi limit for a DFP). This new quantity would thus not adversely impact the safety or the ability of a licensee to decommission a Ge-68/Ga-68 generator.

Relationship of the proposed rulemaking to NRC's Strategic Plan

The proposed rule supports NRC's 2013-2018 Strategic Plan by supporting its Regulatory Effectiveness Strategy 1: Proactively identify, assess, understand, and resolve safety and security issues. The proposed rule supports these activities in the following ways:

- Resolve generic safety and security issues and ensure implementation of enhancements within timeframes commensurate with their risk significance.

  The use of a more up- to-date value for labeling unsealed Ge-68 for limited use in Ge/Ga-68 generators used for medical use and returned to the manufacturer poses no decommissioning safety risk. The lack of decommissioning risk warrants the special circumstance of doing a direct final rule in order to minimize the significant risk of preventing patient access to the medical benefits received from Ga-68 radiopharmaceuticals.

- Emphasize the importance of developing and maintaining an effective nuclear-safety culture for all NRC-regulated activities and for activities regulated by the Agreement States.

The 27-year-old labeling value used to require a DFP which for Ge-68 has resulted in the unintended regulatory impediment for medical use of the Ge/Ga-68 generator. Immediate correction of this unintended regulatory impediment will demonstrate NRC's support of medical safety culture.

The subcommittee's recommendation to the Committee is that the following language be added as a footnote to Appendix B Part 30 -- Quantities[1] of Licensed Material Requiring Labeling.

> [3]This does not include Ge-68 in a Ge-68/Ga-68 medical use generators (limit less than 2 uCi x 10^5) that are returned to the manufacturer at end of use.

The subcommittee believes this recommendation has strong basis to support this regulatory change through the Direct Final Rulemaking process. This process should be initiated as soon as possible by the NRC to eliminate the deleterious effect the DFP process is having on patient access to Ga-68 radiopharmaceuticals.

The ACMUI unanimously endorsed this report and addendum on August 12, 2015.

Germanium-68 (Ge-68) Decommissioning Funding Plan (DFP) Subcommittee

Report: Addendum

August 12, 2015

Submitted by: S. Langhorst; S. Mattmuller

It was after the Subcommittee had submitted it first draft report that the proposed 2 uCi labeling value was determined not to be an appropriate value for all licensees. For example the large university-based medical center on the East Coast as described in the report would still have to prepare a DFP to determine their site-specific financial assurance even at the new proposed 2 uCi labeling value. By following the original methodology for calculating labeling values in Appendix B of Part 30 the Subcommittee proposed a labeling value of 10 uCi for Ge-68. The following questions and answers were reviewed and determined by the ACMUI to substantiate 10 uCi as the proposed labeling value and to provide justification for a direct rule making for the specific case of Ge-68 when contained in a medical use Ge/Ga-68 generator that is decommissioned by return to the manufacturer.

1. *What purpose do the labeling values for Appendix B of Part 30 serve?*

   The labeling values for those licensed materials with half-lives greater than 120 days are used to determine whether the possession limits approved for a license require the licensee to maintain financial assurance for decommissioning, and if so, what amount of financial assurance is required (§ 30.35). The labeling values for those licensed materials with half-lives less than or equal to 120 days serve no purpose.

2. *Where did values for Appendix B of Part 30 come from?*

   Prior to 1994, Appendix B of Part 30 did not exist. Instead, the requirements in § 30.35 referenced the old Appendix C of Part 20 which first appeared in the regulations in 1970. The regulatory history for Appendix B of Part 30 listed at the bottom of that table is the regulatory history of the old Appendix C of Part 20 prior to 1994.

   The current decommissioning funding plan (DFP) regulations in § 30.35 are based on values that were established 45 years ago.

3. *How were values for the old Appendix C of Part 20 derived?*

Description of how the values for the old Appendix C of Part 20 were chosen is specified in the proposed changes to Part 20 and Part 30[3] published in 1968 (33 FR 11414, August 10, 1968):

> "Two basic criteria were used in deriving the quantities. Since inhalation is considered the most likely route of entry into the body, the quantity that would be inhaled by a standard man exposed for 1 year at the highest average concentration permitted in air (by 10 CFR Part 20) for members of the general public was computed. If the radioisotope emits gamma radiation, the quantity that, from a point source, would produce a radiation level of 1 milliroentgen per hour at a distance of 10 centimeters was also computed. The smaller of these two quantities was then logarithmically rounded to the nearest decade, in microcuries, and entered in § 30.71, Schedule B."

4. *Why was Ge-68 not included in the old Appendix C of Part 20?*

The air concentrations of licensed materials permitted in air were based on the International Commission on Radiological Protection Committee II (ICRP 2) recommended values for maximum permissible concentrations[4] . ICRP 2 was published in 1959; Ge-68 was not included in the list of radionuclides. The current Appendix B of Part 30 does not include a specific value for Ge-68 because data published 56 years ago did not include that radionuclide.

5. *Since Ge-68 is not specifically listed in Appendix B of Part 30, what labeling value applies for Ge-68?*

For Ge-68 (half-life 271 days) in unsealed form, the default labeling value for non-alpha emitting radionuclide is used. This default value of 0.1 uCi is used to determine what amount of financial assurance is required by § 30.35 for decommissioning a license possessing Ge-68.

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

[3] Schedule B of Part 30 "Exempt Quantities" was established at the same time as Appendix C of Part 20.
[4] "Report of Committee II on Permissible Dose for Internal Radiation (1959)," Health Physics Journal, Vol 3, Issue 1, April 1959.

Note that if other radionuclides with half-lives greater than 120 days are also allowed to be possessed, then the sum of the ratios for those radionuclides must also be included in this calculation.

6. *Why is there an issue now with Ge-68 possession and financial assurance?*

New Ga-68 radiopharmaceuticals have been developed and are in widespread use in Europe. Currently they are under review by the Food and Drug Administration (FDA) for approval in the United States.

These Ga-68 radiopharmaceuticals have proven to be the new standard for imaging certain cancers called neuroendocrine tumors (NET). In addition to greater diagnostic accuracy these new radiopharmaceuticals provide for greater patient comfort, convenience and a lower radiation dose compared to the current radiopharmaceutical in use today.

Since Ga-68 has a short half-life of 68 minutes, medical use can only be accomplished by use of the Ge/Ga-68 generators in a similar fashion as the Mo/Tc-99m generators. The Ge-68 is designed to remain in the shielded generator and the Ga-68 is eluted from the generator. A Ge/Ga-68 generator can be supplied with 50 millicurie of Ge-68, and this quantity that would trigger the requirement for a DFP. Because a DFP is an extensive and expensive site-specific plan to produce, maintain and review (see Question 12), use of Ge/Ga-68 generators may be limited to a few medical licensees already maintaining a DFP and thus the availability of these valuable radiopharmaceuticals will not be widely offered to patients.

7. *How will decommissioning take place for Ge/Ga-68 generators?*

The Ge-68 in a Ge/Ga-68 generator is for all practical purposes a solid source within a sealed source. At the end of its useful life the generator will be returned to its manufacturer who will be responsible for its final disposal. The medical licensee will have no Ge-68 remaining at its site, hence the cost for decommissioning would not warrant the need to greatly increase the financial assurance needed by the medical licensee.

8. *If Ge-68 had been specifically listed in Appendix B of Part 30, what would the labeling value be?*

One option to choosing the labeling value for Ge-68 is to use the specific labeling value listed in the updated Appendix C of Part 20. This value for unsealed Ge-68 is 10 uCi.

Another option is to calculate the value using the criteria specified in 1968 (see Question 3) and the highest average concentration of Ge-68 permitted in air (by Appendix B Part 20, Table 2, Column 1) for members of the general public, which is 5×10^{-9} uCi/ml. The first criteria calculation is:

$V_1 = 5 \times 10^{-9}$ uCi/ml x 20,000 ml/min x 60 min/hr x 24 hr/day x 365 day = 53 uCi

Considering that the Ge-68 in a Ge/Ga-68 generator is not your typical unsealed source, but is practically a solid within a sealed source, a calculated value based on air concentrations is very conservative.

The second criteria calculation involves use of a gamma exposure calculation. Germanium-68 does not decay by emission of gammas, but its daughter, Ga-68, decays with photon emissions. The exposure rate constant[5] for Ga-68 is 5.43 R-cm^2/mCi-hr. The second criteria calculation is:

$$V_2 = (0.001 \text{ R/h} \times 100 \text{ cm}^2 \times 1000 \text{ uCi/mCi}) / 5.43 \text{ R-cm}^2\text{/mCi-hr} = 18 \text{ uCi}$$

So, logarithmically rounding to the nearest decade for the smaller of these two values, V_2, would mean the labeling value for Ge-68 should be 10 uCi.

This is the same value that was listed for labeling unsealed Ge-68 in the new Appendix C of Part 20 in 1994. Hence, 10 uCi would seem to be the appropriate labeling value for Ge-68.

9. *If 10 uCi is proposed for the specific labeling value for Ge-68 used in a Ge/Ga-68 generator meant for medical use, then that means the labeling value used would increase by a factor of 100 and the DFP trigger level would increase from 10 mCi to 1 Ci. Is that safe?*

Yes. Remember, the labeling values in Appendix B of Part 30 are only used to determine the level of financial assurance needed for decommissioning. These values are not used for any other regulatory requirement, and definitely are not used as any kind of radiological criteria for allowing a formerly licensed site to be released for unrestricted use under § 20.1402.

Also, the substantial safety inherent to a Ge/Ga-68 generator (see Question 7) makes its use will far less likely to result in residual contamination than the unsealed uses allowed for other radionuclides[6] listed in Appendix B of Part 30 which also have a labeling quantity of 10 uCi. The cost for decommissioning a Ge/Ga-68 generator would not warrant the need to greatly increase the financial assurance needed by the medical licensee.

10. *What would it mean to a medical licensee if the labeling value for Ge-68 used in a Ge/Ga-68 generator meant for medical use was changed to be 10 uCi?*

A value of 10 uCi used for Ge-68 to determine what amount of financial assurance is required by § 30.35 for decommissioning a license possessing unsealed Ge-68 would be as follows.

---

[5] Smith, D.S and Stabin, M.G., "Exposure Rate Constants and Lead Shielding Values for Over 1,100 Radionuclides," Health Physics Journal, Vol 102, No 3, March 2012.

[6] Examples of other radionuclides (half-life) with 10 microcurie labeling value in Appendix B of Part 30: Sb-125 (2.8 years), Ba-133 (10.6 years), Ca-45 (163 days), Cs-137 (30 years), Cl-36 (300,000 years), Mn-54 (312 days), Ni-63 (101 years), and Zn-65 (244 days).

Ge-68 Possession Limit (mCi)	Financial Assurance required (§ 30.35)
Less than or equal to 10	none
Greater than 10 to 100	$225,000
Greater than 100 to 1,000	$1,125,000
Greater than 1,000	Decommissioning Funding Plan is required to determine the amount of financial assurance

Note again that if other radionuclides with half-lives greater than 120 days are also allowed to be possessed, then the sum of the ratios for those radionuclides must also be included in this calculation. Licensees providing Ga-68 diagnostic procedures would be required to maintain at least $225,000 in financial assurance which is more than enough funding to ship their final generators back to the manufacturer. Medical licensees who do large numbers of these Ga-68 diagnostic procedures, or who are approved to possess other greater than 120-day half-life radionuclides, would most likely be required to maintain at least $1,125,000 in financial assurance. Again, this amount of financial assurance is more than adequate funding to decommission Ge/Ga-68 generators.

11. What is a decommissioning funding plan?

Decommission means to remove a facility or site safely from service and reduce residual radioactivity to a level that permits (1) release of the property for unrestricted use and termination of the license or (2) release of the property under restricted conditions and termination of the license (§ 20.1003). A decommissioning funding plan (DFP) is a site-specific cost estimate to fully decommission a license and is used to set a license-specific amount of financial assurance the licensee is required to maintain.

12. What does it mean to develop and maintain a DFP?

As stated in § 30.35(e)(1), each DFP is required to be submitted to and approved by the NRC. The DFP must contain the following:

- a detailed cost estimate, in an amount reflecting –
    - cost of an independent contractor to perform all decommissioning activities;
    - cost of meeting criteria of unrestricted release (§ 20.1402), or for certain provisions, restricted use release (§ 20.1403);
    - the volume of onsite subsurface material containing residual radioactivity that will require remediation; and
    - an adequate contingency factor.
- identification and justification for all key assumptions used;

- description of method of assuring funding for decommissioning, including cost adjustments and associated funding levels periodically over the life of the facility;
- certification by the licensee that financial assurance in the amount of the cost estimate; and
- a signed original of the financial instrument.

The DFP is required to be updated and resubmitted for NRC approval at the time of license renewal and at intervals not to exceed 3 years. The DFP must update the information submitted with the original or prior approved plan, and must specifically consider the effect of the following events on decommissioning costs:

- spills of radioactive material producing additional residual radioactivity in onsite subsurface material;
- waste inventory increasing above the amount previously estimated;
- waste disposal costs increasing above the amount previously estimated;
- facility modifications;
- changes in authorized possession limits;
- actual remediation costs that exceed the previous cost estimate;
- onsite disposal; and
- use of a settling pond.

The use of a DFP is applicable for licenses with complicated or extensive possession limits so that the financial assurance is adequate and continually updated to ensure decommissioning funds will be available to complete license termination. Developing and maintaining a DFP is time consuming and costly in the personnel time needed meet compliance with all the regulatory requirements.

Review of DFPs is also costly for the NRC and Agreement States personnel. As an example, Washington University in St. Louis (WU) has a Broad Scope Type A Medical Use license and an Accelerator Production license issued by the NRC. WU maintains a DFP and financial assurance in the amount of $6.77 million. Not counting the cyclotron and large sealed source decommissioning costs, WU's possession of greater than 120-day half-life radionuclides requires about $2 million in financial assurance. The last WU DFP approved by the NRC was submitted by WU September 2009. WU submitted an updated DFP December 2010 when a large sealed source device was added to the license. No review questions were requested by the NRC. Another updated DFP was submitted February 2013 when the license was renewed. NRC review questions were sent to WU September 2014 and answered by WU in December 2014. As of August 2015, NRC had not completed review of the 2010 or 2013 DFP updates. WU is required to submit the next DFP update by February 2016.

This example of the time and resources needed by the NRC to review a DFP provides indication of what a large burden the NRC and the Agreement States be asked to take on if more DFPs were required. Given the ease and low cost of decommissioning a medical use Ge/Ga-68

generator, requiring a DFP for this generator use does not make fiscal sense for the medial licensee or for the regulator.

13. *What would happen if the label value for Ge-68 in medical use Ge/Ga-68 generators was not changed from the current generic label value of 0.1 uCi?*

    Licensees who did not already maintain a DFP would be required to develop and maintain a DFP in order to request possession of even one medical use Ge/Ga-68 generator. The cost to develop and maintain a DFP would be prohibitive to most medical licensees and the Ga-68 diagnostic procedures would not be available to most patients

    That would mean patients would have to continue with an inferior radiopharmaceutical that would result in a less accurate diagnosis, take an extra day to complete the study and would result in a higher radiation dose to the patient. It would also mean that the current average length of time for a correct diagnosis for NET patients would not be improved.

14. *What would happen if the label value for Ge-68 in medical use Ge/Ga-68 generators was changed to 2 uCi as originally suggested?*

    If 2 uCi was chosen as the Ge-68 in medical use Ge/Ga-68 generators, a medical licensee who is not currently required to maintain any level of financial assurance would then be required to maintain $1,125,000 as shown here.

Ge-68 Possession Limit (mCi)	Financial Assurance required (§ 30.35)
Less than or equal to 2	none
Greater than 2 to 20	$225,000
Greater than 20 to 200	$1,125,000
Greater than 200	Decommissioning Funding Plan is required to determine the amount of financial assurance

    This amount of financial assurance does not seem logical given the ease and low cost of decommissioning a medical use Ge/Ga-68 generator. If a medical licensee has other radionuclides with half-lives greater than 120 day, a value of 2 uCi for Ge-68 results in 25% towards the ratio sum for each 50 mCi possession limit. Broad scope medical licensees who have structured their license possession limits so that they remain at the $1,125,000 level for financial assurance may not be able to absorb 25% - 50% towards the ratio sum without then having to do a DFP. This is the very situation that would still require the large university-based

medical center on the East Coast that is described in the report (and others like it) to prepare a DFP.

Instead, as shown in Question 10, use of 10 uCi for Ge-68 in a medical use Ge/Ga-68 generator would result in 10% toward the ratio sum for each 50 mCi possession limit. Most broad scope medical licensees who have structured their license possession limits so that they remain at the $1,125,000 level for financial assurance will most likely be able to absorb 10% - 20% towards the ratio sum and still remain at the $1,125,000 level for financial assurance.

Given the ease and low cost of decommissioning a medical use Ge/Ga-68 generator, use of 10 uCi for Ge-68 in a medical use Ge/Ga-68 generator would maintain financial assurance without hindering the development of Ga-68 radiopharmaceuticals.

Conclusion -

The cost of decommissioning a medical use Ge/Ga-68 generator does not warrant the need for, and the additional licensee and regulator costs associated with, a site-specific DFP. Use of the current generic label value for Ge-68 will continue to limit patient access to the use and further development of Ga-68 radiopharmaceuticals. Changing to 10 uCi as the specific label value for Ge-68 used in medical use Ge/Ga-68 generators will guarantee that there is more than adequate financial assurance for decommissioning and will increase patient safety. With the current Ga-68 radiopharmaceuticals under FDA review, 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.

Thus, the Committee changed its recommendation to be stated as follows; the following language be added as a footnote to Appendix B Part 30 -- Quantities[1] of Licensed Material Requiring Labeling.

> [3]This does not include Ge-68 in a Ge-68/Ga-68 medical use generators (limit less than 10 uCi x 10^5) that are returned to the manufacturer at end of use.