

# Development of a Traceable Calibration Methodology for Solid $^{68}\text{Ge}/^{68}\text{Ga}$ Sources Used as a Calibration Surrogate for $^{18}\text{F}$ in Radionuclide Activity Calibrators

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We have developed a methodology for calibrating  $^{68}\text{Ge}$  radioactivity content in a commercially available calibration source for activity calibrators in a way that is traceable to the national standard. Additionally, the source was cross-calibrated for equivalent  $^{18}\text{F}$  content by direct comparison with the national standard for  $^{18}\text{F}$  in the same geometry. **Methods:** Sources containing standardized  $^{68}\text{GeCl}_4$  or  $^{18}\text{F}$ -FDG solutions were prepared at the National Institute of Standards and Technology (NIST) with mock syringe blanks used in the construction of a commercially available epoxy-based  $^{68}\text{Ge}$  calibration source. These sources and several NIST-constructed epoxy-based  $^{68}\text{Ge}$  mock syringes were then used as artifact standards to determine calibration factors for NIST-maintained activity calibrators and secondary standard ionization chambers to enable calibration of the actual commercial sources. A direct comparison between the solution-based  $^{68}\text{Ge}$  sources and the  $^{18}\text{F}$ -FDG sources allowed for an empiric determination of the relative response for these radionuclides in several commercial activity calibrators. Potential measurement effects due to differences between the solution composition and the epoxy and theoretic  $^{68}\text{Ge}$ -to- $^{18}\text{F}$  response ratios were studied by Monte Carlo simulation. **Results:** The calibration factors developed in this study enabled NIST to calibrate epoxy-based mock syringe sources with a relative combined standard uncertainty of 0.52%. The direct comparisons of the  $^{68}\text{Ge}$  and  $^{18}\text{F}$  standards in the various ionization chambers allowed the activity to be expressed in terms of equivalent  $^{18}\text{F}$  activity with a relative combined standard uncertainty of about 0.9%. **Conclusion:** The ability for NIST to calibrate these epoxy-based mock syringes enabled, for the first time to our knowledge, the direct traceability to the national  $^{68}\text{Ge}$  standard to be established for this type of source. Through a direct comparison with the NIST  $^{18}\text{F}$  standard, the determination of the relative response ratios in activity calibrators enabled the equivalent  $^{18}\text{F}$  activity to be determined in a way that was also traceable to the national  $^{18}\text{F}$  activity standard.

**Key Words:**  $^{18}\text{F}$ ; calibration;  $^{68}\text{Ge}$ ; PET; standards

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**T**he ability to obtain quantitative data from PET studies has led to an increase in its use in drug discovery. The comparability of results of biodistribution studies across a population of patients in multiple clinical sites using imaging data acquired with different scanners and analyzed with different algorithms requires the data to be linked to a common standard to reliably draw conclusions about differences in patient response. Moreover, the ability to discern small changes in tumor metabolism during a course of treatment can be realized only if there is a way to ensure that the calibrations of all the associated measurement instrumentation (e.g., activity calibrators, commonly known as dose calibrators, and PET scanners) are constant over time.

The National Institute of Standards and Technology (NIST) is the national metrology institute of the United States and is responsible for the development and dissemination of standards of all physical quantities, including radioactivity. Measurement standards are generally designated as primary if their measurements are made with techniques that do not require the use of any other standards to arrive at an activity value. In contrast, secondary standards are obtained when a measured activity value relies on the use of a primary standard as a calibration, such as in the case of an activity calibrator.

Although NIST has developed primary standards for positron-emitting radionuclides such as  $^{18}\text{F}$  and  $^{62}\text{Cu}$  in the past (1–4), it is nearly impossible to prepare and distribute artifact standards of these radionuclides because of their short half-lives (on the order of minutes). As a potential solution, NIST recently developed a primary standard for the relatively long-lived (half-life, 270.95(16) d) radionuclide  $^{68}\text{Ge}$  in equilibrium with its positron-emitting decay daughter,  $^{68}\text{Ga}$  (5), for the first time. Although the decay properties

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of  $^{68}\text{Ga}$  are not identical to those of  $^{18}\text{F}$ , there are enough similarities that it has been suggested that  $^{68}\text{Ge}/^{68}\text{Ga}$  could be used as a reasonable surrogate, assuming that the necessary correction factors can be determined. Such correction factors would strongly depend on the instrument and the geometry in which the source is measured.

A  $^{68}\text{Ge}$ -based calibration source, designed to replicate a 6-mL plastic syringe filled with 3 mL of solution, was recently developed by RadQual, LLC, and is intended to be used to calibrate activity calibrators for the measurement of  $^{18}\text{F}$ . The purpose of this study was to develop a methodology for calibrating these sources for  $^{68}\text{Ge}$  activity that is traceable to the national standard for  $^{68}\text{Ge}$  and to experimentally determine the response of the  $^{68}\text{Ge}$ -based calibration source relative to the response of a source of  $^{18}\text{F}$ -FDG in such a way as to maintain the links between the national standards for both  $^{68}\text{Ge}$  and  $^{18}\text{F}$ .

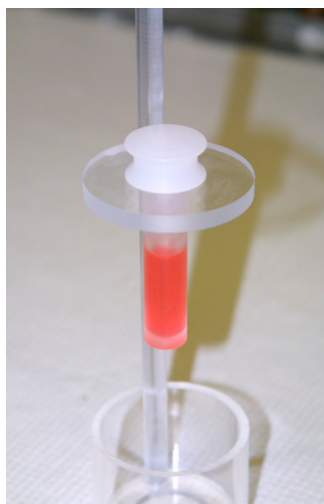
## MATERIALS AND METHODS

### Calibration of $^{68}\text{Ge}$ Mock Syringe Sources

Stock solutions of  $^{68}\text{GeCl}_4$  were obtained from International Isotopes Idaho, Inc. The solutions, and derivatives thereof, were calibrated for radioactivity content at NIST by either primary or secondary methods, as described in Zimmerman et al. (5). All dilutions were performed using a carrier solution containing nominally 45  $\mu\text{g}$  each of nonradioactive  $\text{GeCl}_4$  and  $\text{GaCl}_3$  per gram of solution in 0.5 M HCl. All nuclear and atomic data used as input for the analysis of experimental data were taken from the Decay Data Evaluation Project evaluation (6).

The mock syringe source consisted of nominally 5 MBq of  $^{68}\text{Ge}$  distributed in a commercially available epoxy encapsulant (Emerson & Cuming) in a proprietary container constructed from poly(methyl methacrylate) (Fig. 1) designed to mimic a 6-mL plastic syringe containing 3 mL of  $^{18}\text{F}$ -FDG. The container body is nominally 6.5 cm long and has an outside diameter of about 1.6 cm and a wall thickness of 0.23 cm. The empty mock syringes used for preparing the sources at NIST were supplied by RadQual, LLC.

Preliminary experiments involving the gravimetric mixing of the epoxy and a precalibrated  $^{68}\text{GeCl}_4$  solution indicated that the between-source variability in the total activity of  $^{68}\text{Ge}$  in the epoxy



**FIGURE 1.** Photograph of NIST-constructed epoxy-based mock syringe source. Source was prepared using production blanks used to construct RadQual Benchmark mock syringes. Coloring was added only to highlight filling volume.

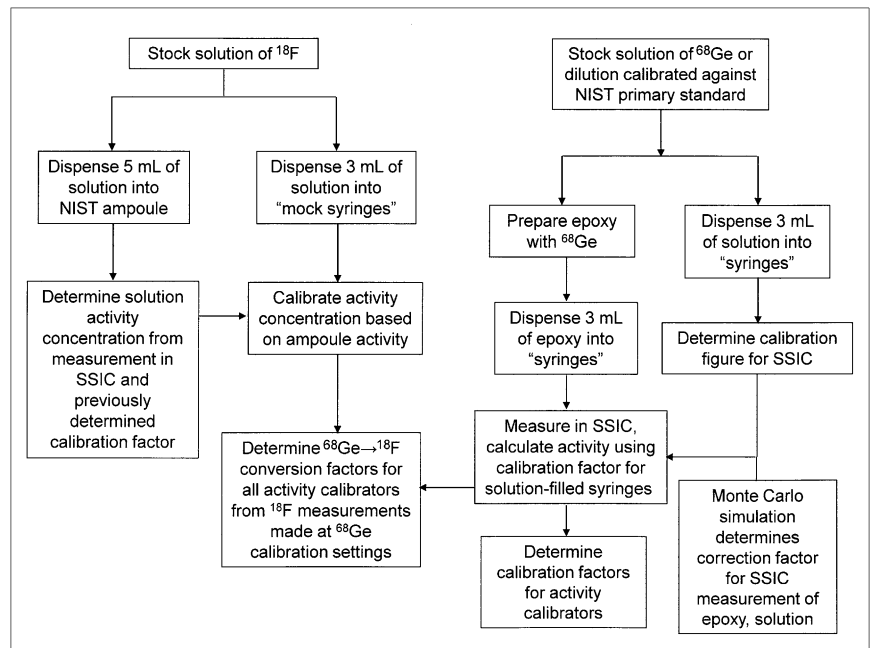
was more than 1% when 3-mL aliquots were dispensed from each of 2 independently prepared epoxy batches. This variability was judged to be too high to rely solely on the activity concentration in the epoxy to calculate the total activity. Therefore, a methodology to directly calibrate the activity in each individual source was developed using a secondary standard ionization chamber. The generalized scheme for this procedure is shown in Figure 2.

A series of 5 liquid-filled mock syringe standards was prepared by dispensing 3 mL of a previously calibrated  $^{68}\text{Ge}$  solution into each source blank, which was weighed before and after filling to obtain the dispensed mass. The total activity (typically  $\sim 5$  MBq) in each source was calculated from the dispensed mass and the calibrated  $^{68}\text{Ge}$  activity concentration. A calibration factor (in units of  $\text{pA}\cdot\text{MBq}^{-1}$ ) for the NIST-maintained Vinten 671 secondary standard ionization chamber (SSIC) was determined for each of the sources using this value. To ensure the consistent placement of the source within the SSIC, the sources were measured in a specially constructed thin-walled plastic holder at the bottom of the source dipper. Each measurement in the SSIC consisted of 10 repeated measurements of the ionization current for each source, taken at 2-s intervals. A total of 1,000 measurements of the background current, also at 2-s intervals, and 10 measurements of the ionization current produced by a  $^{226}\text{Ra}$  reference source were also obtained. In addition to the SSIC measurements on the mock syringes, each source was measured in the NIST-maintained AtomLab and Capintec activity calibrators in the syringe-holder position for the respective source dippers, to determine the appropriate calibration settings for these instruments using this geometry.

Two sets of  $^{68}\text{Ge}$  epoxy-filled mock syringes (for a total of 8) were prepared on 2 different occasions and with 2 different master  $^{68}\text{GeCl}_4$  solutions as follows:

- The 2 components of the epoxy were gravimetrically added to a polyethylene dropper bottle in mass ratios (mass resin or mass hardener) as specified by the manufacturer.
- Precalibrated  $^{68}\text{GeCl}_4$  solution was gravimetrically transferred to the contents of the dropper bottle. The amount of solution did not exceed the limit of 50  $\mu\text{L}$  per gram of epoxy, as specified by the manufacturer.
- The mixture was mechanically stirred at 140 revolutions per minute for a minimum of 20 min.
- Nominally 3 mL of  $^{68}\text{Ge}$  epoxy were transferred to a preweighed source blank.
- Point sources were prepared between each syringe dispensing as an additional check of homogeneity. This was done by gravimetrically depositing a drop of the  $^{68}\text{Ge}$  epoxy from the dropper bottle onto a piece of 0.006-cm-thick polyester tape, which was stretched over a standard NIST ring mount (0.5-mm-thick aluminum annulus, 3.8-cm inside diameter, and 5.4-cm outside diameter). After the epoxy hardened (overnight), another piece of polyester tape was stretched over the ring mount as a cover.
- The mock syringes were reweighed after all of the sources had been dispensed to obtain the mass of added  $^{68}\text{Ge}$  epoxy and solvent sealed.

Using the calibration factor determined for the liquid-filled mock syringes in the SSIC, we measured the  $^{68}\text{Ge}$  epoxy mock syringes and calculated the activity. To investigate possible measurement effects due to differences in composition and density between the epoxy and the  $^{68}\text{Ge}$  solution, simulations of the SSIC with the



**FIGURE 2.** Preparation and calibration scheme for  $^{68}\text{Ge}$  and  $^{18}\text{F}$ -FDG mock syringe sources, including linkage between  $^{68}\text{Ge}$  and  $^{18}\text{F}$  national standards.

liquid- and  $^{68}\text{Ge}$  epoxy-filled mock syringes were performed using the PENCYL user code from the PENELOPE (7,8) Monte Carlo code and the DOSRZnrc user code from EGSnrc MP (9–11).

For the simulations, the dimensions and materials of the SSIC were obtained from the technical drawings of the manufacturer. Cross sections for all of the materials, with the exception of the pressurized nitrogen in the SSIC and the epoxy, came directly from each code package's materials database. The cross sections for the pressurized nitrogen were calculated from each code package's materials database using their respective utility programs, assuming molecular nitrogen at standard temperature and a pressure of  $101.325\text{ N}\cdot\text{cm}^{-2}$  (10 atm). Similarly, the cross sections for the epoxy were calculated using the composition provided by the manufacturer (John Gilbert, Emerson & Cuming, oral communication, 2008) and each code package's respective utility program. The positron spectrum for  $^{68}\text{Ga}$  was calculated using the SPEBETA code (12) and the output reformatted so as to be compatible with the DOSRZnrc and PENCYL input data file formats. Each DOSRZnrc simulation was run for a total of  $5 \times 10^6$  primary (positron) events, whereas the PENCYL simulations were limited to  $10^6$  primaries to limit the time required for each simulation. The cutoff energies for photons and electrons (positrons) were 100 eV for the PENCYL calculations and 1 keV for the DOSRZnrc simulations.

Once the total activities in the  $^{68}\text{Ge}$  epoxy mock syringes were determined, those values were used to determine the correct dial settings for the NIST-maintained AtomLab and Capintec activity calibrators. At the same time, the liquid-filled mock syringes were remeasured to confirm the dial settings previously determined for those sources.

#### Linkage to $^{18}\text{F}$ Standard

To relate the measurements of the  $^{68}\text{Ge}$  epoxy mock syringes in the activity calibrators to a measurement of  $^{18}\text{F}$ -FDG solution in the same geometry, an additional experiment was performed that involved gravimetrically filling a series of 3 mock syringe blanks with  $^{18}\text{F}$ -FDG (IBA Molecular North America). The filling procedure was identical to that for the  $^{68}\text{Ge}$  solution-filled mock syringes described above. A NIST standard flame-sealed 5-mL

ampoule was also gravimetrically prepared at the same time. The activity concentration of the  $^{18}\text{F}$ -FDG solution was determined by measuring the ampoule in the SSIC and applying a calibration factor that was derived in an earlier experiment (3). The experimental parameters for the  $^{18}\text{F}$ -FDG SSIC measurements were identical to those described above for the  $^{68}\text{Ge}$  sources. As a consistency check, the ampoule was also measured in each of the Capintec activity calibrators at a dial setting of 475, which we determined during the same experiment in which the SSIC calibration factor was determined.

Measurements were then made in the NIST-maintained AtomLab and Capintec activity calibrators to determine the relative responses of the instruments to the  $^{18}\text{F}$ -FDG mock syringes. A single measurement was made at the previously determined  $^{68}\text{Ge}$  mock syringe setting for each respective chamber and at 5 additional settings within  $\pm 20$  dial setting units ( $\pm 5$  units for the AtomLab), which could allow for the determination of a new calibration factor for  $^{18}\text{F}$  in this geometry for those chambers.

As a check of experimentally measured relative responses of  $^{18}\text{F}$  and  $^{68}\text{Ge}$ , an additional Monte Carlo simulation was performed using DOSRZnrc for  $^{18}\text{F}$  solution in the mock syringe geometry in the SSIC and compared with the results of the  $^{68}\text{Ge}$  liquid-filled mock syringe simulations. The positron spectrum for  $^{18}\text{F}$  was calculated using the SPEBETA code, and the simulation parameters were the same as those for the  $^{68}\text{Ge}$  calculations described above.

## RESULTS

All evaluations of measurement uncertainties throughout this work follow accepted conventions used by the NIST Radioactivity Group and are in accordance with those recommended by the principal metrology organizations (13). All individual uncertainty components are given as estimated experimental SD (or SD of the mean, if appropriate) or quantities assumed to correspond to SD regardless of the method used to evaluate their magnitude. All uncertainties cited in this article are standard uncertainties, corresponding to 1 uncertainty interval.

## <sup>68</sup>Ge Source Calibration

From the measurements of the solution-filled mock syringe sources, a calibration factor of  $9.98 \pm 0.05$  pA·MBq<sup>-1</sup> was obtained for the SSIC. This factor was calculated as the average of the calibration factors determined for the 4 mock syringes. The uncertainty was estimated from the quadratic addition of components due to the primary standardization of the <sup>68</sup>Ge (0.34%), measurement variability for 10 determinations of the ionization current of a single source (0.05%), uncertainty on the sample mass (0.05%), decay correction ( $2.4 \times 10^{-3}\%$ ), repeatability on 2 sets of determinations of calibration factors for the 4 mock syringes (0.33%), and background current variability ( $1.2 \times 10^{-2}\%$ ).

The <sup>68</sup>Ge epoxy-filled mock syringe was developed to mimic as closely as possible a 6-mL plastic syringe filled with 3 mL of solution. Therefore, it was expected that the same calibration factor that was derived for the liquid-filled mock syringe in the SSIC could also be used to calculate the activity contained in the epoxy-filled mock syringes. However, because the compositions and densities of the epoxy and the <sup>68</sup>Ge solution are not identical, it was necessary to verify this and to estimate the effect of these differences on the ionization chamber response. Verification and estimation were achieved by comparing the calculated absorbed dose in the ionization gas of the SSIC for the 2 source configurations. The absorbed dose, which is directly proportional to the chamber response, was calculated for each simulation by summing the tallied dose (in Gy/particle) in the pressurized nitrogen regions for the epoxy and solution mock syringe cases. The results from both PENELOPE and EGSnrc agreed and indicated a difference in absorbed dose in the gas of 0.1% between the solution and the epoxy, with a relative standard uncertainty on each simulation of about 0.9% (due primarily to the limited counting statistics). Thus, no measurable difference in activity determination for the epoxy-filled mock syringes would be expected by use of the calibration factor derived for the solution-filled mock syringes. Because the magnitude was estimated using a Monte Carlo model (i.e., not measured) and had a magnitude that was small in comparison to its own uncertainty, no correction was applied to the activity results. Because of the large uncertainty on the magnitude of the effect, an estimate of it was included in the uncertainty budget for the <sup>68</sup>Ge epoxy source activity.

The activities of the <sup>68</sup>Ge epoxy-filled mock syringes, as determined from measurements in the SSIC and expressed as of the experiment reference time, are presented in Table 1. The activities are also expressed in terms of activity units per gram as a demonstration of the achievable homogeneity of these sources. The combined standard uncertainties given are estimated from an evaluation of the components described in Table 2.

The activities of the epoxy-based mock syringes that were obtained from the SSIC measurements were then used to derive dial settings for the Capintec and AtomLab activity calibrators for this geometry. The average dial settings

**TABLE 1.** Measured and Massic Activities for NIST-Prepared <sup>68</sup>Ge Epoxy-Filled Mock Syringes

Source identifier	Total activity (Bq)	Massic activity (Bq·g <sup>-1</sup> )
E3S1	$(2.28 \pm 0.01) \times 10^6$	$(6.97 \pm 0.04) \times 10^5$
E3S2	$(2.30 \pm 0.01) \times 10^6$	$(6.98 \pm 0.04) \times 10^5$
E3S3	$(2.41 \pm 0.01) \times 10^6$	$(6.92 \pm 0.04) \times 10^5$
E3S4	$(2.26 \pm 0.01) \times 10^6$	$(6.80 \pm 0.04) \times 10^5$
E3S5	$(2.02 \pm 0.01) \times 10^6$	$(6.76 \pm 0.04) \times 10^5$
ES1	$(6.45 \pm 0.03) \times 10^5$	$(1.98 \pm 0.01) \times 10^5$
ES2	$(7.03 \pm 0.04) \times 10^5$	$(2.05 \pm 0.01) \times 10^5$
ES3	$(6.58 \pm 0.03) \times 10^5$	$(2.06 \pm 0.01) \times 10^5$

Data are presented as of common reference date. All uncertainties are estimated on basis of uncertainty components presented in Table 2. Massic activity values have additional uncertainty component of magnitude 0.1% that is due to uncertainty in mass of added epoxy.

obtained for each chamber, along with their combined standard uncertainties, are presented in Table 3.

## Determination of Response Factors Relating <sup>68</sup>Ge Activity to <sup>18</sup>F

The total activity of <sup>18</sup>F-FDG in each source was calculated and compared with the activity reading at the calibration settings derived for the <sup>68</sup>Ge epoxy-filled mock syringes (Table 3) using the activity concentration, as measured in the SSIC, and the measured dispensed mass for each mock syringe source. The activity measurements in the Capintec chambers confirmed that the <sup>18</sup>F SSIC value was within experimental uncertainties.

The relative responses for the <sup>18</sup>F-FDG mock syringes in each of the NIST-maintained activity calibrators at their respective dial settings determined for the <sup>68</sup>Ge epoxy-filled mock syringes are presented in Table 4.

From the data in Table 4, it was possible to derive an experimental relative response factor of  $1.054 \pm 0.010$  to relate the observed <sup>68</sup>Ge activity to an equivalent <sup>18</sup>F activity in these instruments. In this case, the uncertainty was calculated from the quadratic addition of the SD on the 4 values listed in Table 4 (0.31%) combined with the average standard uncertainty for the determination of a single correction factor (0.88%).

The relative response ratio of <sup>18</sup>F to <sup>68</sup>Ge in the SSIC calculated using the Monte Carlo simulations was 1.053, including the differences in the positron branching ratios, with a standard uncertainty of about 0.9% (again, due primarily to relatively low counting statistics), which is in excellent agreement with the experimental value. No additional radiations emitted in the decays of <sup>18</sup>F, <sup>68</sup>Ga, or <sup>68</sup>Ge (such as the x-rays emitted in the decay of <sup>68</sup>Ge or <sup>68</sup>Ga) were included in these simulations. However, it is expected that their contributions to the total absorbed dose in the nitrogen would be low because of self-absorption in the source and in the thickness of the aluminum walls of the chamber.

**TABLE 2.** Uncertainty Components Evaluated for Determination of Total Activity Contained in NIST-Prepared <sup>68</sup>Ge Epoxy-Filled Syringes

Component, $u_i$	Comment	Magnitude (%)
SSIC chamber calibration factor	Combined standard uncertainty on activity of solution-filled sources used to derive calibration factor	0.47
Current measurement repeatability	SD of mean on 10 measurements of current for single source	0.21
Background variability	SD of mean on 1,000 measurements of background current for single source	2.00E-02
Decay correction	Standard uncertainty in half-life (0.059%) over measurement decay interval	2.40E-03
Current measurement reproducibility	SD on 2 measurements of each source; typical value	0.04
Combined ( $u_c = \sqrt{\sum u_i^2}$ )		0.52

## DISCUSSION

### Calibration of <sup>68</sup>Ge Mock Syringes

Our first approach to developing a calibration methodology for the mock syringes was to mix the epoxy and <sup>68</sup>Ge standardized solution gravimetrically and use the calculated activity concentration and the measured dispensed mass to calculate the activity contained in the mock syringes. However, from the data in Table 1, it is clear that the <sup>68</sup>Ge distribution within the epoxy is not homogeneous, which is the primary assumption made in using such an approach. For the series E3S1–E3S5, the SD on the activity concentration is about 1.5%, whereas the SD for the separately prepared series ES1–ES3 is about 2%. There appears to be a trend toward a decrease in the concentration of the <sup>68</sup>Ge as the time between end of mixing and preparation of the mock syringe increases. This is evident in the data for series E3S1–E3S5, in which this time interval ranged from 5 to 25 min. This trend is not observed in series ES1–ES3, possibly because all 3 sources were prepared within 5 min of each other and within 10 min of the end of mixing.

To ensure that this apparent drop in activity over time was not due to volatilization of the <sup>68</sup>Ge out of the epoxy, an additional batch of epoxy with <sup>68</sup>Ge was prepared and placed in the SSIC for 1 h, with current measurements acquired every 30 s. No decrease in the total activity of the mixture was observed during this time period, except for that attributed to radioactive decay. With this information, we postulated that the drop in activity was due to a concentration gradient arising from incomplete mixing of the <sup>68</sup>Ge in the epoxy, with the highest concentration at the top of the dispenser bottle.

Although this could perhaps have been avoided with either longer or more vigorous mixing, additional problems in dispensing would probably have resulted from the introduction of more air into the epoxy and higher viscosity of the epoxy due to the additional setting time. The fact that the activity of each source was different (the procedure developed in this study measured the contained activity in each source individually) was not an issue because these sources were going to be used internally only by NIST for the development of the calibration factors necessary to calibrate manufacturers' sources having the same configuration. The data in Tables 1 and 2 demonstrate that this procedure now enables NIST to calibrate these types of

epoxy-filled mock syringe sources with a combined standard uncertainty of 0.52%.

### Cross-Calibration for <sup>18</sup>F and Implications for Source Usage

According to the manufacturer, the <sup>68</sup>Ge calibration source is intended to be used as a long-lived surrogate for calibrating activity calibrators for <sup>18</sup>F activity in a geometry approximating a 6-mL syringe containing 3 mL of liquid. That is, the equivalent <sup>18</sup>F activity contained in the source can be calculated from the calibrated <sup>68</sup>Ge activity value, and this value could then be used to determine the correct activity calibrator setting for <sup>18</sup>F in that geometry. However, this is possible only if the relative response of the chamber to both <sup>68</sup>Ge and <sup>18</sup>F in the same geometry is accurately known.

In this study, the relative response ratio was  $1.054 \pm 0.010$  for this specific geometry using the same activity calibrators at the same dial settings as were used in the measurements for the <sup>68</sup>Ge mock syringe sources. This result should be interpreted as indicating that a 3-mL sample of <sup>18</sup>F-FDG in this geometry will give a reading in these activity calibrators (at the <sup>68</sup>Ge setting) that is 5.4% higher than an equivalent volume of <sup>68</sup>Ge having the same activity. The experimental ratio was confirmed by Monte Carlo simulation, which indicated that although the differences in maximum positron energy ( $E_{\beta, \max} = 1,899$  keV for <sup>68</sup>Ga and 633 keV for <sup>18</sup>F) result in <sup>68</sup>Ge giving a 2.4% higher response per emitted

**TABLE 3.** Experimentally Determined Calibration Settings for NIST-Maintained Capintec and AtomLab Radionuclide Activity Calibrators for <sup>68</sup>Ge Epoxy-Filled Mock Syringes

Activity calibrator	Calibration setting
Capintec CRC-12	452 ± 1
Capintec CRC-15R	442 ± 1
Capintec CRC-35R	444 ± 1
AtomLab 100	10.8 ± 0.1

Settings were determined by adjusting setting value until correct calibrated activity value was displayed on instrument readout. Values displayed are averages of 8 determinations of calibration factor (1 for each syringe source), and uncertainty is calculated from SD of mean of those 8 measurements.

**TABLE 4.** Ratios of Response of Commercial Activity Calibrators to  $^{18}\text{F}$  and  $^{68}\text{Ge}$  in Mock Syringe Geometry at Appropriate  $^{68}\text{Ge}$  Dial Setting (Table 3) for Each Specific Calibrator

Source	CRC-12	CRC-15	CRC-35R	AtomLab 100
E6FS1	1.0513	1.0486	1.0559	1.0512
E6FS2	1.0638	1.0546	1.0564	1.0523
E6FS3	1.0583	1.0510	1.0563	1.0535
Average	$1.0578 \pm 0.0063$	$1.0514 \pm 0.0030$	$1.0562 \pm 0.0003$	$1.0523 \pm 0.0012$

Ratios were obtained by dividing activity readout from chamber for each  $^{18}\text{F}$ -FDG source by NIST-calibrated activity for that source. Uncertainty is SD on 3 determinations of response ratios.

positron, this effect is actually overcompensated for by the much higher positron branching ratio in the  $^{18}\text{F}$  decay, resulting in a higher response for  $^{18}\text{F}$ .

The construction of the mock syringe is somewhat different from a clinical syringe in terms of wall material and thickness and in the densities of the solution and epoxy. These differences could influence the accuracy of the transfer of the calibration from the calibration geometry to the one used clinically. A systematic evaluation of such an effect lies outside of the scope of this study and was not performed. We did, however, compare the equivalent  $^{18}\text{F}$  activities calculated from the calibrated  $^{68}\text{Ge}$  activity for 2 of the NIST-constructed mock syringes to the readings obtained at activity calibrator settings derived for  $^{18}\text{F}$  in previous experiments (3,4) for different syringes geometries. For 2 sources measured in 3 of our activity calibrators, the difference ranged from +0.04% to -1.7%, with an average of -0.8% and SD of 0.6%. This value lies within the uncertainties on the equivalent  $^{18}\text{F}$  activity calculated from the  $^{68}\text{Ge}$  source (0.9%) and the activity calibrator manufacturer's stated uncertainty of typically 2% for measurements in their chambers. Therefore, it is difficult to state definitively if this uncertainty is significant in a clinical setting. Such an evaluation would need to be made by the institution using the calibration sources, taking into account their goals for measurement accuracy and acceptable levels of uncertainty.

Also, the relative response factor was determined on the basis of a measurement using the appropriate dial setting for the  $^{68}\text{Ge}$  epoxy-filled mock syringe. The ratio at other calibration settings or in other activity calibrator models has not been measured by NIST and therefore cannot be certified. The results presented herein should be considered valid only for the specific mock syringe sources described and for the actual chambers maintained by NIST. Users of the data provided in this article are strongly encouraged to verify the validity of such data on their own systems.

## CONCLUSION

A series of experiments aimed at developing secondary calibration standards for  $^{68}\text{Ge}$  in an epoxy-filled mock syringe geometry has been performed, thereby giving NIST the capability of calibrating epoxy-filled mock syringe  $^{68}\text{Ge}$  calibration sources such as the RadQual Benchmark with a combined standard uncertainty of 0.52%. Calibration

factors were determined for this source in various AtomLab and Capintec model activity calibrators using several NIST-manufactured sources of this same geometry.

Using  $^{18}\text{F}$ -FDG solutions calibrated at NIST, we directly compared the response of the AtomLab and Capintec radionuclide activity calibrators with  $^{18}\text{F}$ -FDG relative to this particular  $^{68}\text{Ge}$  epoxy-filled mock syringe calibration source. A relative response factor of  $1.054 \pm 0.010$  was derived from these measurements to relate the observed  $^{68}\text{Ge}$  activity to an equivalent activity of  $^{18}\text{F}$ -FDG. This ratio was independently confirmed by Monte Carlo simulation.

## ACKNOWLEDGMENTS

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