SIR-Spheres Activity Measurements Reveal Systematic Miscalibration

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The purpose of this work was to perform an independent and National Institute of Standards and Technology–traceable activity measurement of ^{90}Y SIR-Spheres (Sirtex). γ-spectroscopic measurements of the ^{90}Y internal pair production decay mode were made using a high-purity germanium detector. **Methods:** Measured annihilation radiation detection rates were corrected for radioactive decay during acquisition, dead time, source attenuation, and source geometry effects. Detection efficiency was determined by 2 independent and National Institute of Standards and Technology–traceable methods. **Results:** Measured SIR-Spheres vials ($n = 5$) contained more activity than specified by the manufacturer calibration; on average, the ratio of measured activity to calibrated was 1.233 ± 0.030. Activity measurements made using 2 distinct efficiency calibration methods agreed within 1%. **Conclusion:** The primary SIR-Spheres activity calibration appears to be a significant underestimate of true activity.

Key Words: TARE; radioembolization; radiopharmaceutical therapy

Dosimetry-guided radiopharmaceutical therapy is gaining traction in nuclear medicine and adjacent fields. Several agents have been approved with a requirement of dosimetry (^{131}I-metaiodobenzylguanidine, ^{90}Y TheraSphere [Boston Scientific]), but even agents that do not currently carry a dosimetry mandate (e.g., ^{177}Lu-DOTA-TATE and ^{90}Y SIR-Spheres [Sirtex]) are increasingly being used under dosimetry-guided treatment paradigms. This increase is evidenced by a recent survey indicating that a majority (64%) were clinically administering SIR-Spheres according to absorbed dose rather than body surface area–derived activity, which is the current U.S. Food and Drug Administration–approved label method (1). Additionally, combination-therapy approaches have been gaining popularity, particularly in combining radiopharmaceutical therapy with external-beam radiotherapy, immunotherapy, or both (2–5). As this trend continues, it is critical that our field develop standard practices for measurement, delivery, and verification of absorbed radiation dose. Perhaps the most fundamental consideration is whether we are administering a quantity of radioactive material that is consistent with what is prescribed by the authorized user.

In this work, we describe a series of 2 independent high-purity germanium (HPGe) spectrographic measurements—grounded to National Institute of Standards and Technology (NIST)–traceable sources and measurement—to determine the activity contained within SIR-Spheres vials before patient treatment in relation to the manufacturer-provided activity calibration.

MATERIALS AND METHODS

SIR-Spheres and Manufacturer Calibration

^{90}Y SIR-Spheres are received from the manufacturer in a glass vial within a lead pig. With agitation, the spheres are uniformly suspended in about 5 mL of sterile water; however, within about 2 min of nonagitation the microspheres settle to the bottom of the vial, with approximately 4 mL of water supernatant. Vials can be received from the manufacturer with varying activity levels, by way of delivery on various days before the date and time of reference calibration; however, the same number of spheres ($\pm5\%$) is present within a vial regardless of the activity provided. Each vial is specified by the manufacturer to contain 3 GBq (81 mCi) $\pm$ 10% at the date and time of calibration (often on the day of treatment at 6:00 PM Eastern Standard Time). Vials expire 24 h after the calibration date and time, regardless of the precalibration date of receipt.

Although the nominal activity of any individual vial is specified as 3 GBq $\pm$ 10%, on request the manufacturer will provide a certificate of measurement of the vial at the production facility. This certificate contains an exact activity measurement of a particular vial within the manufacturer's own ion chamber, decay-corrected to the date and time of calibration. Activity within this report is provided with 4 significant figures (e.g., 3.004 GBq) and without any associated measurement-uncertainty specification. This certificate, and the associated activity vial, are the primary mechanisms by which a user site or radiopharmacy establishes dose calibrator dial settings before initiation of a clinical program. This procedure was performed at the University of Iowa in 2012 for initial dose calibrator configuration. An additional certificate was obtained for one of the samples measured in this work (received April 26, 2021) to confirm that the University of Iowa dose calibrator remained traceable to the manufacturer's ion chamber. A single dose calibrator (Capintec CRC-15R) was used for all measurements described here.

HPGe Spectrometry

^{90}Y activity measurements were performed by HPGe spectroscopic measurements (Ortec GEM20P4-70) via counting of the 511-keV annihilation emission produced following the 32-parts-per-million internal pair production decay mode of ^{90}Y (6). Energy and peak-shape calibration was performed using NIST-traceable sources (^{241}Am, ^{57}Co, ^{137}Cs, ^{60}Co, and ^{152}Eu; SD, 1.16%; Eckert and Ziegler). A custom high-density-polyethylene source holder (1 cm thick, density = 0.966 ± 0.009 g/cm^3) was manufactured and used to ensure local positron annihilation during

spectral acquisition. This source holder and an example patient vial are shown in Figure 1.

All patient vials were measured at a distance of 210 cm from the detector (surface-to-surface distance), with acquisition durations of 3–6 h. All samples were measured 1 d before the calibration date and thus were expected to be in the range of 4–5 GBq. Despite the lack of abundant γ-emissions, the high levels of activity and associated Bremsstrahlung emissions induced relatively high dead times during data collection—ranging between 22.5% and 25.6% depending on the sample, as estimated by Ortec HPGe electronics. Because of the importance of dead-time correction in these measurements, a separate experiment was performed to validate the accuracy of dead-time estimation provided by Ortec. Details on this measurement are included in the supplemental section (available at http://jnm.snmjournals.org). Spectral peak areas were determined using the SAMPO algorithm, which uses a well-established peak-fitting method (7).

Efficiency Calibration

Detector efficiency was calibrated via 2 distinct methods.

In method 1, NIST-traceable sources (^{241}Am, ^{57}Co, ^{137}Cs, ^{60}Co, and ^{152}Eu; Eckert and Ziegler) were used to establish absolute detection efficiency as a function of energy, with the sources in the same position as the patient vial during counting. Because this efficiency estimate does not account for self-attenuation of 511-keV emissions within the source vial and holder, Monte Carlo simulations were performed to determine the appropriate self-absorption correction factor. Simulations were performed in Monte Carlo N-particle code, version 6.2, and verified using the Geant4 Application for Tomographic Emission. Details on these simulations are provided in the supplemental materials.

In method 2, a NIST-traceable calibrated quantity of ^{18}F ($\sim$37 MBq in 3 mL) was placed within an empty SIR-Spheres vial, and spectral acquisition was performed under conditions identical to those for ^{90}Y measurements, including geometry and dead time. Under these conditions, a 511-keV efficiency calibration was obtained by comparing the observed 511-keV count rate with the known emission rate within the ^{18}F sample. ^{18}F samples were calibrated using a ^{68}Ge/^{68}Ga standard tied to a NIST ^{18}F measurement for dose calibrator configuration (8). The ^{18}F sample was assayed under calibrated conditions (3 mL in a 5-mL syringe) with quantitative transfer and decay correction before spectrometry.

Activity Determination and Measurement Uncertainty

^{90}Y activity was determined from the measured peak area, detector live time, detection efficiency, and literature value of the internal pair production branching ratio (6). The branching ratio measured by Selwyn et al. (6)—(31.86 ± 0.47) × 10^{-6}—was used for this work; this ratio generally agrees with other measurements (9), as well as being the value recommended by the Decay Data Evaluation Project, last updated in 2015 (10). Second-order corrections were applied for radioactive decay during spectral acquisitions, background 511-keV count rate, and geometry effects (^{18}F vs. ^{90}Y). These corrections are detailed in the supplemental materials.

Determination of measurement uncertainty in this work followed NIST guidelines (11) and the International Organization for Standardization expression of uncertainty (12). Type A uncertainty in this experiment consisted of statistical uncertainty in the measured 511-keV peak area for each sample. Several sources of type B uncertainty were characterized, including Monte Carlo statistical uncertainty, glass vial thickness (inter- and intravial variability), source holder thickness, positron range effects, dead-time correction precision, positron branching ratio uncertainty, and several additional factors relating to detection efficiency determination. All uncertainties are specified in terms of SE (1 SD), and propagation followed the standard root-sum-of-squares method (13).

RESULTS

The local dose calibrator at the University of Iowa agreed with the manufacturer's certificate of calibration within 0.5%, suggesting that historic dose calibrator readings (Capintec CRC-15R; dial setting, 56 × 10) have been a reasonable surrogate for the manufacturer's activity calibration. A review of the last 100 patient vials received by the University of Iowa revealed that the manufacturer has been consistent with its product label of 3.00 GBq (±10%) at the date and time of calibration, according to activity measurements using a dose calibrator. These data are presented in Figure 2. Of 100 patient vials, only one was outside the manufacturer-specified range.

Activities measured by HPGe assay were substantially higher than manufacturer-specified values (Table 1). The estimated ratio of absolute activity to what has been specified by the manufacturer was 1.233 ± 0.030. This final value represents the average of results for all samples and for both method 1 and method 2 within each sample.
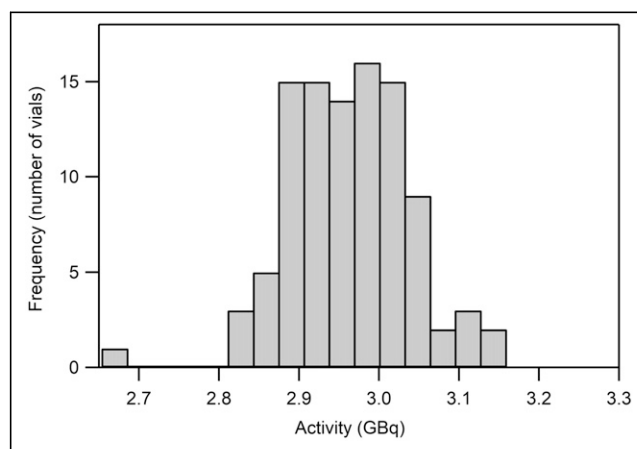

FIGURE 1. Photograph of custom high-density-polyethylene source holder and example SIR-Spheres patient vial.

FIGURE 2. Distribution of activities received from manufacturer at time of calibration, as measured by manufacturer-traceable dose calibrator (n = 100, received between February 2019 and April 2021).

TABLE 1
Summary of Measured Patient Vial Activities, Decay-Corrected to Date and Time of Calibration

Sample	Manufacturer (GBq)	HPGe method 1 (GBq)	HPGe method 2 (GBq)	HPGe/manufacturer ratio
1	2.65	3.25 (±3.8%)	3.28 (±3.4%)	1.232
2	2.84	3.43 (±4.2%)	3.46 (±3.8%)	1.212
3	2.99	3.73 (±4.0%)	3.77 (±3.6%)	1.254
4	3.00	3.67 (±4.0%)	3.71 (±3.6%)	1.229
5	3.08	3.80 (±4.2%)	3.83 (±3.8%)	1.240
Average				1.233 ± 0.030

Activity quantitation by methods 1 and 2 provided virtually identical results, with method 2 yielding values about 1.0% higher than method 1. Agreement between these methods suggests that the experimentally determined 511-keV detection efficiency (number measured/number emitted) is robust to experimental approach. Background 511-keV count rate (0.090 ± 0.006 cps) was small in comparison with experimental samples (~2.2 cps). Despite estimated detector dead times of 22.5%–25.6%, correction for these effects was accurate when explicitly accounting for a slight bias above approximately 10% dead time (the supplemental materials provide details).

Variation in the ratio of HPGe-determined activity to dose calibrator–determined activity across samples was consistent with statistical uncertainty within individual measurements. Measurement durations of 3–6 h per patient vial provided statistical uncertainty of 2.5%–3.1% in measured 511-keV peak areas. Components of overall measurement uncertainty are listed in Table 2, with uncertainty being largely dominated by counting statistical uncertainty (~2.5%), uncertainty in the internal pair production branching ratio of ^{90}Y (1.48%) (6), efficiency calibration (method 1, 1.9%), and ^{18}F calibration (method 2, 1.2%). When the measurement was performed multiple times, statistical uncertainty was reduced to an acceptable level in the final calibration specification. Uncertainty in the final ratio (±2.47%) includes uncertainty in measurements and systematic effects, correction having been applied for all known systematic effects.

DISCUSSION

We have identified a miscalibration associated with the SIR-Spheres product. The ratio of our measured activity levels to those provided by the manufacturer calibration is 1.233 ± 0.030. This indicates that about 23% more activity has been administered to patients than anticipated and prescribed. Although this result is potentially a regulatory concern (per Nuclear Regulatory Commission criteria for reportable medical events, ±20% from prescribed), this finding is not immediately concerning from a medical or ethical standpoint.

TABLE 2
Components of Measurement Uncertainty from Representative Patient Vial (Sample 1)

Uncertainty	Type A (methods 1 and 2)	Type B (method 1)	Type B (methods 1 and 2)	Type B (method 2)
Net peak area	2.50%			
Glass density and thickness (intervial variation)			0.40%	
Monte Carlo statistical uncertainty		0.05%		
Glass density and thickness (intravial variation)		0.70%		
High-density polyethylene density and thickness		0.12%		
Volume and activity-distribution effects		0.50%		0.91%
Efficiency calibration (energy interpolation)		1.50%		
Efficiency calibration (traceable source activities)		1.16%		
Positron range effects (simulated vs. ^{90}Y)		1.28%		
Dead-time correction			0.10%	
^{90}Y positron branching ratio			1.48%	
Positron range effects (^{18}F vs. ^{90}Y)				0.75%
^{18}F activity calibration				1.00%
^{18}F decay correction and residual				0.63%
Total	2.50%	2.45%	1.54%	1.67%
Average of methods 1 and 2				3.29%

TABLE 3
Dose Calibrator Settings and Prior Data

Reference	Dose calibrator dial setting	Implied calibration error
Current SIR-Spheres calibration*	56 × 10 (model, CRC-15R)	—
Selwyn, 2008 (15)	—	~23%–31%
Moore, 2007 (16)	24 × 10 (model, CRC-15R)	29%
Ferreira, 2016 (17)	32 × 10 (model, CRC-25R)	~20%[†]
This work	29 × 10 (model, CRC-15R)	23%

*Current SIR-Spheres calibration dial setting may differ by institution and instrument; however, 56 × 10 is setting used on University of Iowa CRC-15R to match manufacturer activity specification.
[†]Estimated using CRC-15R; true discrepancy may differ slightly when using correct model (CRC-25R).

From discussion with the manufacturer, this discrepant activity standard has been consistent throughout the availability of this product, including early trials and associated data reviewed by the U.S. Food and Drug Administration for approval (14). This statement is corroborated by a report in 2008 by Selwyn et al. (15) indicating that a SIR-Spheres vial was found to have 26% ± 1.8% more activity than the nominal manufacturer value (3.00 GBq ± 10%) (15). In his measurement, Selwyn et al. did not compare directly against the manufacturer activity calibration; however, on the basis of our data presented in Figure 2, there is a good chance that the calibrated quantity of activity was between 2.9 and 3.1 GBq, thus implying a miscalibration on the order of 23%–31%. Additional evidence was presented in a 2007 abstract by Moore et al. (16), wherein a calibrated quantity of ^{90}Y-chloride was used to determine appropriate dose calibrator settings for SIR-Spheres. Their reported dose calibrator setting (24 × 10, Capintec CRC-15R) was evaluated on the University of Iowa CRC-15R, and this dial setting displayed about 29% more activity than the manufacturer calibration (56 × 10 on our particular device). Work by Ferreira et al. (17) established accurate SIR-Spheres calibration factors for the Vinten 671 (0.0678 pA/MBq) and the Capintec CRC-25R (dial setting 32 × 10). Although a CRC-25R was not available for comparison at our institution, use of 32 × 10 on the University of Iowa CRC-15R displays about 20% more activity than the manufacturer calibration. These reports (15–17), summarized in Table 3, are consistent with our findings and support the theory that a systematic calibration error has been present for SIR-Spheres over approximately the last 14 y.

According to the manufacturer, more than 100,000 patients have been treated with SIR-Spheres worldwide, with more than 1,000 health-care providers currently offering this treatment. This treatment is generally regarded as an excellent option for patients with hepatic tumors. A systematic miscalibration of administered activity has little to no bearing on the accepted safety and efficacy of this agent; however, this finding will have significant scientific implications moving forward. Additional efforts by the manufacturer are needed to precisely establish an absolute activity standard for SIR-Spheres. These changes should come about in collaboration with at least one institution capable of making absolute activity measurements, such as NIST or another group that has already made significant progress toward establishing a SIR-Sphere measurement standard (18,19).

Existing publications addressing liver dose–toxicity relationships with glass and resin microspheres have consistently demonstrated a lower dose toxicity threshold from resin spheres. Work by Chiesa et al. showed that mean liver doses in excess of 70 Gy from glass microspheres were associated with more than a 50% probability of normal-tissue complications (20). By comparison, data from resin microspheres indicate that a 50% probability of normal-tissue complications is associated with a mean liver dose of 52 Gy (95% CI, 44–61 Gy) (21). With the assumption that prior studies were conducted using manufacturer-recommended activity calibration techniques, the miscalibration identified in our work indicates a somewhat narrower toxicity discrepancy—approximately 64 Gy (resin) versus 70 Gy (glass) when correcting for this effect. This finding necessitates reevaluation of published dosimetry data and interpretations thereof.

The discovery of this miscalibration points to a broader issue in the field of radiopharmaceutical therapy: there is a lack of generalizable methods for independent verification of activity calibration by end users, such as what is done in radiation oncology for linear accelerator and sealed source assay. Efforts should be made to extend the capabilities of currently accredited dosimetry calibration laboratories to include unsealed sources, or a new mechanism for independent calibration verification should be established.

CONCLUSION

The primary SIR-Spheres activity calibration appears to be an underestimate of true activity. HPGe spectroscopic measurements of annihilation radiation emissions have provided an estimate of 1.233 ± 0.030 for the ratio of true activity to activity specified by the manufacturer calibration. This finding should be independently verified, and the manufacturer should take steps to establish an accurate and traceable activity standard.

DISCLOSURE

An early version of this article was provided to Sirtex Medical Limited for technical review and comment. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: How do measured SIR-Spheres activities compare with the nominal manufacturer calibration?

PERTINENT FINDINGS: The nominal SIR-Spheres activity calibration appears to be an underestimate of true activity. HPGe spectroscopic measurements of annihilation radiation emissions have provided an estimate of 1.233 ± 0.030 for the ratio of true activity to activity specified by the manufacturer calibration.

IMPLICATIONS FOR PATIENT CARE: A revised activity calibration is needed, which will result in changes to clinical activity prescribing patterns.

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