Calibration Setting Numbers for Dose Calibrators for the PET Isotopes ^{52}Mn , ^{64}Cu , ^{76}Br , ^{86}Y , ^{89}Zr , ^{124}I

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Abstract

For PET radionuclides, the radioactivity of a sample can be conveniently measured by a dose calibrator. These devices depend on a “calibration setting number”, but many recommended settings from manuals were interpolated based on standard sources of other radionuclide(s). We conducted HPGe gamma-ray spectroscopy, resulting in a reference for determining settings in two types of vessels containing one of several PET radionuclides. Our results reiterate the notion that in-house, experimental calibrations are recommended for different radionuclides and vessels. (78/80 words)

Keywords: dose calibrator; ionization chamber; calibration setting number; instrumentation; radiation measurements; ^{52}Mn ; ^{64}Cu ; ^{76}Br ; ^{86}Y ; ^{89}Zr ; ^{124}I

1. Introduction

Many PET imaging agents that are currently in development, including peptides, antibodies, and nanoparticles, have biological half-lives of hours to days, so they require positron-emitting radiolabels with longer half-lives than traditional PET isotopes, such as ^{11}C or ^{18}F . Other isotopes such as ^{64}Cu , ^{86}Y , ^{89}Zr , and ^{124}I , satisfy these criteria and are currently used as radiolabels for compounds in preclinical and clinical research (Ikotun and Lapi, 2011; Nayak and Brechbiel, 2009; Wadas et al., 2010). For studies using any of these isotopes, it is critical to obtain accurate measurements of activity at numerous stages of the PET study, including: immediately following target irradiation, chemical separation, dispensing, radiolabelling, and pre-injection. These radioactivity measurements are commonly measured in laboratory and clinical settings using a dose calibrator, which provides fast results for the measurement of the radioactivity of a sample. This type of benchtop instrument has a small enough footprint and a small enough cost to be commonly installed in many different rooms that might be used during the workflow from cyclotron to injection.

The user manuals provided by Capintec (2007, 2015) for the dose calibrators that were used in this investigation provided a good explanation of the physics of radiation measurement that are employed by these models of gas ionization dose calibrators. We only briefly summarize these explanations here. Dose calibrators measure the radioactivity of a sample based on the rate at which it emits ionizing photon radiation—X-rays, gamma-rays, or other photons (e.g., from positron annihilation). With a few exceptions, particle radiation—alphas, betas, and positrons—are not penetrating enough to cause ionization in the gas chamber. In many models of dose calibrators, the radioactive sample is lowered into the center of a cylindrical sealed chamber

containing a gas. Photons in the 100-2,000 keV energy range do not directly produce the ionization signal for the dose calibrator, but rather they interact with the wall and/or gas of the chamber to release electrons, and these secondary electrons ionize the gas in the chamber enough to produce the electric signal that is measured by the device. Electric current is created in a circuit within the dose calibrator, and the magnitude of this current is directly proportional to the activity of the isotope that emitted the radiation (for similar sample geometries). In the dose calibrators used in this investigation, the gas in the chamber was argon, which is also used in many other gas ionization dose calibrators.

Since the radiation dose rates vary widely by isotope, the accuracy of these instruments relies on using the correct calibration setting for the isotope being measured. For ionization chambers connected to older, analog control units, a dial setting adjusts a potentiometer to change the gain in the detector for the isotope being measured (IAEA). In newer, digital dose calibrators, a “calibration setting number” (represented by the variable N_A in certain user manuals) simply adjusts the digital output of the unit (Capintec, 2007, 2015; Chandra, 2011). In both generations of dose calibrators, numerous commonly used isotopes have pre-programmed settings that can be selected, but a custom calibration setting number must be entered (or dialed) for other isotopes. Many calibration setting numbers are recommended by Capintec in user manuals, but the vast majority of these values were calculated using an empirical linear fit equation that was based upon the detector response to only two isotopes in a single geometry (Capintec, 2007, 2015). Specifically, these measurements were conducted for reference sources consisting of 5 mL of solution containing ^{57}Co or ^{60}Co in a glass ampoule with 0.6 mm wall thickness, obtained from the United States National Institute of Standards and Technology (NIST) (NIST, 2011; Capintec, 2007, 2015).

Consequently, several publications have endeavored to experimentally determine new calibration setting numbers for various models of Capintec dose calibrators, sample geometries, and radionuclides. To measure reference activities, these investigations have used various radioanalytical techniques: HPGe detector (Beattie *et al.*, 2014; Coursey *et al.*, 1993; Zimmerman *et al.*, 2001), NaI(Tl) detector (Zimmerman *et al.*, 2002), $4\pi\beta$ liquid scintillation ($4\pi\beta$ -LS) (Cessna *et al.*, 2008; Mo *et al.*, 2006; Zimmerman and Cessna, 2000; Zimmerman *et al.*, 1999), or a different gas ionization chamber (Tyler and Woods, 2002, 2003). Some of the calibration setting numbers that were determined in these studies yielded activity readouts that were dramatically different from the activity readout from recommended settings. In at least one case, Capintec officially changed its recommended calibration for an isotope: Based on the results of Zimmerman, *et al.* (2001) and later Cessna, *et al.* (2008), the recommended setting number for ^{18}F was changed from 439 to 472 for NIST ampoules and 484 for 3 mL plastic syringes (Capintec, 2009). Furthermore, the calibration setting numbers for the same isotopes in the same dose calibrator models were often greater for samples with larger volumes. Geometry effects are even more pronounced for isotopes that emit low-energy gamma-rays (Tyler and Woods, 2003); or positrons or beta particles (Capintec, 2007, 2015) because these radiations are more susceptible to systematic errors resulting from attenuation or scattering, respectively.

We acknowledge that some facilities in radiochemistry and nuclear medicine may rely solely on Capintec dose calibrators to measure activity—without access to a high-precision reference measurement instrument, such as a HPGe detector. In Section 2.3, we performed gamma-ray spectroscopy using a HPGe detector to quantify the amount of radioactivity in samples that served as references for the experimental determination of calibration setting numbers for two different sample geometries containing the PET isotopes ^{52}Mn , ^{64}Cu , ^{86}Y , ^{89}Zr ,

⁷⁶Br and ¹²⁴I. The two geometries that we tested were 2 mL microcentrifuge tubes, which are widely measured in dose calibrators for radiochemistry work, and 10 cc (10 mL) syringes, which are commonly measured in dose calibrators before injection of a radiopharmaceutical.

2. Materials and Methods

2.1. Materials

Ultrapure water (~18 MΩ) was obtained from a Millipore system (Billerica, Massachusetts, United States) and was used for diluting aliquots of radioactivity. 2 mL microcentrifuge tubes and 10 cc syringes were purchased from Fisher Scientific (Pittsburgh, Pennsylvania, United States). All ¹²⁴I was purchased from 3D Imaging (Maumelle, Arkansas, United States).

2.2. Isotope Production

All other isotopes used in this work were produced on-site by (*p,n*) reactions in solid targets that were bombarded with protons from the CS-15 cyclotron (The Cyclotron Corporation, Berkeley, California, United States) at Washington University School of Medicine in St. Louis (WUSM). Various methods (Table 1) were carried out by remotely-controlled automated modules inside of lead hot cells to separate the following isotope products from the

corresponding bulk solid target material: ^{64}Cu (Kume et al., 2012; McCarthy et al., 1997), ^{76}Br (McCarthy et al., 1999; Tolmachev et al., 1998), ^{86}Y (Avila-Rodriguez et al., 2008; Yoo et al., 2005), and ^{89}Zr (Holland et al., 2009; Meijs et al., 1994; Wooten et al., 2012). Manganese-52 was produced by bombarding a natural Cr foil target with protons (Wooten et al., 2015), followed by digesting the Cr foil in hydrochloric acid with no further purification. Iodine-124 was produced in a manner similar to methods that were published by Knust, *et al.* (2000) and Sheh, *et al.* (2000). For each isotope, aliquots were taken and diluted with ultrapure water as needed for gamma-ray spectroscopy (Section 2.3) or dose calibrator measurements (Section 2.4).

2.3. Gamma-Ray Spectroscopy

The activity per volume of the product solution was calculated based on gamma-ray spectroscopy results from one of two Canberra (Meriden, Connecticut, United States) brand HPGe detector systems: Detector 1 (model GC1818 with 18.9% efficiency) and Detector 2 (model GC2018 with 24.5% efficiency). Each detector was connected to a digital spectrum analyzer (DSA; model: DSA-1000) and operated by the *Gamma Acquisition & Analysis* module of the *Genie 2000* spectroscopy software package (v. 3.3). The HPGe detector was calibrated for energy and efficiency based on the full-absorption photopeaks from a mixed-gamma reference source (Eckert & Ziegler Analytics, Atlanta, Georgia, United States). This calibration source consisted of a 2 mL skirted microcentrifuge tube that contained eight radioisotopes in a hardened epoxy, which was an identical geometry to the 2 mL microcentrifuge tubes used for counting emissions from our diluted isotope products.

For each isotope considered in this study, an aqueous solution containing the isotope was serially diluted in 2 mL microcentrifuge tubes until the Ge detector yielded a dead time <5%. The dilution was produced in triplicate, and each of these three tubes was scanned long enough to acquire $\geq 10^3$ counts for the gamma-ray with the highest branching ratio, which was typically 10-30 min of detector live time. In the spectroscopy results, we identified at least one full-absorption photopeak that corresponded to an identifying gamma-ray energy (E_γ) that was emitted by the isotope being measured. Gamma-ray energy(ies) with the highest branching ratio(s) without also being emitted by a metastable isomer (e.g., $E_\gamma=1,434$ keV from ^{52m}Mn) were used for analysis. The number of counts and detector efficiency for the selected peak were used to calculate the activity per volume, assuming no decay during counting because the counting period was short (<5%) relative to the isotope's half-life using the following equation:

$$A = \frac{N_c}{\varepsilon_c I_\gamma t_l}, \quad (1)$$

where A is the activity (Bq); N_c is the number of counts (net peak area) for the full-absorption photopeak; ε_c is the counting efficiency for the detector at the corresponding gamma-ray energy (dimensionless); I_γ is the branching ratio for the corresponding gamma-ray (dimensionless); t_l is the detector live time during gamma-ray counting. The results calculated using Equation 1 were decay-corrected to an arbitrary time in the past for all three tubes, averaged together, and then multiplied by the dilution factor to determine the activity per volume of the original product solution at that common time. This value was then used to calculate the activity per volume in the product solution at the time when the samples would be prepared for the dose calibrator measurement (Section 2.4).

2.4. Dose Calibrator Measurements

Calibration setting numbers were determined from measurements using two models of dose calibrators from Capintec (Ramsey, New Jersey, United States): a model CRC-15R or a model CRC-25R. Characteristics of both of these models are given in Table 2, and they use identical calibration setting numbers (Capintec, 2007, 2009, 2015). For each isotope, one activity between 10-1,000 μCi was selected for measurement in a dose calibrator. Based on the activity per volume calculated from the gamma-ray spectroscopy results, the activity was decay-corrected to the approximate time of measurement in the dose calibrator. Then, the appropriate volume containing the activity was transferred into either a 2 mL microcentrifuge tube or into a 10 cc syringe. The final volume in these vessels was approximately 1 or 8 mL, respectively. The time from pipetting to the end of the final measurement in the dose calibrator was less than 15 min., so decay during that period was negligible for the isotopes studies.

Each sample was placed in the dose calibrator, and the calibration setting number was adjusted until the screen displayed the expected activity based on the gamma spectroscopy results (corrected for dilution and radioactive decay). During these measurements, the precision of the dose calibrator was set to read to the nearest 1 μCi . For some isotopes that emitted high or low dose rates of gamma radiation, it was necessary to find a calibration setting number that caused the control unit to display a multiple of the expected value so divisions or multiplication of the readout by an integer correction factor obtained a meaningful result. When using these dial settings to measure an unknown amount of radioactivity, the readout value would be divided or multiplied by the correction factor for that isotope, such as $\div 2$, $\times 2$, $\times 10$, and $\times 100$, to yield the final activity readout (A_{RO}). For some of our experiments, the sample was removed from the dose calibrator and replaced in a different orientation to account for variations in the positioning of the

vessel within the well of the dose calibrator. For these experiments where only one valid setting was recorded, we conservatively assumed an uncertainty of ± 5 setting numbers to manufacture a range of values. Additionally, for ^{52}Mn , ^{64}Cu , and ^{124}I , the calibration setting number was varied over a large range to observe the effect on activity readout on a wider scale.

2.5. Analysis and Uncertainty Analysis

The entire dose calibrator had an instrumental uncertainty of $\pm 2\%$ (Capintec, 2007, 2015). Since the activity is directly proportional to the activity readout in the local range of calibration setting numbers, we calculated 2% of the maximum in each range, and added or subtracted it to the maximum or minimum of each range to get new values, $N_{A_{min}}$ and $N_{A_{max}}$. If the displayed value needed to be multiplied or divided by a factor, the number was adjusted 2% by the same factor. The midpoint of this new range, $N_{A_{mid}}$, was calculated as the mean of $N_{A_{min}}$ and $N_{A_{max}}$ for that trial, and the uncertainty of this midpoint was $(N_{A_{max}} - N_{A_{min}})/2$. If the vessel was placed in the dose calibrator multiple times, the midpoints from each placement were averaged. The uncertainty in this mean resulted from propagating the individual uncertainty from each placement using the following equation:

$$\delta N_A^2 = \left(\frac{1}{n}\right)^2 \sum_{i=1}^n \delta N_{A_i}^2, \quad (2)$$

where δN_A is the uncertainty in the average; n is the number of trials; and δN_{A_i} is the uncertainty in each value that was averaged together. Equation 2 applies the total differential equation for the

propagation of small uncertainties to the equation for the arithmetic mean, if all uncertainties are uncorrelated (Arras, 1998; Croarkin; Ku, 1966).

Dose calibrator measurements were performed on vessels in triplicate, each resulting in an average result with uncertainty. These results across the three vessels were averaged, and the uncertainty in each final result was obtained by propagating the uncertainties from the individual vessels through Equation 2 (This time, with $n=3$). The final average result was rounded to the nearest integer (because all dial settings are integers), and the uncertainty was accordingly rounded up to the nearest integer to be conservative. These results are the final values and uncertainties that are shown in Table 3.

3. Results

Our results for calibration setting numbers for the Capintec dose calibrators are shown in Table 3 for our six isotopes, both in 2 mL microcentrifuge tubes and in 10 cc syringes. Table 3 also shows the gamma factor (Γ) for each of these isotopes, calculated by Smith and Stabin (2012) to express the dose rates for various isotopes based on a weighted average of gamma-ray energies and branching ratios—including annihilation photons. All results were greater than the recommended values found in the user manuals to varying degrees. This was interesting because the recommended values were interpolated from results based on 5 mL calibration sources, which would be near the midpoint of the two volumes.

For comparison, we measured each of the isotopes in a 10 cc syringe using our result for the calibration setting number and also the recommended value, and the percent difference relative to the measurement using the new value was calculated. These percentages of difference varied significantly (Table 3), and other published works reported (Table 4) that activities measured using recommended calibration setting numbers can differ slightly (~1-10%) or greatly: +50% for ^{90}Y (Coursey et al., 1993); +45% and -42% for ^{125}I in different geometries (Zimmerman et al., 2002); and +35% for ^{111}In (Ceccatelli et al., 2007). In the majority of published studies listed in Table 4, the activity measured using recommended settings would overestimate the amount of activity that was present in the sample. For isotopes that emitted low or high enough total radiation to require a correction factor, that value is also listed in Table 3.

4. Discussion

For selected isotopes and geometries, the activity readout over a wide range of calibration setting numbers was also recorded. These data were plotted in Fig. 1 and demonstrate some sort of inverse relationship of activity readout to calibration setting number across small and large ranges, respectively. These isotopes represented a variety of gamma-ray dose rates, such as ^{52}Mn , ^{64}Cu , and ^{124}I , all in 2 mL microcentrifuge tubes. Readout activity was normalized to the largest value that was measured using the calibration setting numbers in that experiment for that radionuclide. It is important to be aware of these relationships because the fitted equations can be

used to calculate the correct activity of a sample in case the incorrect setting is accidentally used in a measurement. Therefore, when using the dose calibrator, the calibration setting number used should be recorded in case rescaling is necessary in the future.

Using gamma-ray spectroscopy results as a reference, calibration setting numbers for using Capintec dose calibrators to measure the activity of six PET isotopes: ^{52}Mn , ^{64}Cu , ^{76}Br , ^{86}Y , ^{89}Zr , and ^{124}I were determined experimentally for 2 mL microcentrifuge tubes and 10 cc syringes. In many cases, results were significantly different from the calibration setting numbers recommended by the manufacturer. Since the CRC-15R and CRC-25R models of dose calibrators from Capintec were used, results can be used directly for that family of models, including: 15R, 15W, 25R, 25W, 127R, and Ultra-R (Capintec, 2009). However, since the manufacturer's recommended settings are interpolated from other measurements that used a standard glass NIST source geometry, and because results show significant effects of sample geometry for several isotopes, we recommend utilizing a reference sample or high-precision reference measurement—such as HPGe gamma spectroscopy—to experimentally determine calibration setting numbers for various geometries and materials involving dose calibrator use.

In most cases, calibration setting numbers differed from those recommended in the user manual, which meant that using the recommended calibration settings could result in activity measurements higher or lower than expected. Additionally, settings determined for the 10 cc syringes were consistently greater than for the 2 mL geometry. Our results reiterate the widely known fact that experimentally determined dose calibrator settings for various radionuclides and sample geometries are necessary for accurate measurements of radioactivity. These settings have potentially significant implications for radiochemistry experiments, as well as dosimetry for pre-

clinical and clinical applications of radionuclides, including the PET radionuclides that were examined in this work.

5. Conclusion

Using gamma-ray spectroscopy results as a reference, we have experimentally determined calibration setting numbers for using certain Capintec dose calibrators to measure the activity of six PET isotopes: ^{52}Mn , ^{64}Cu , ^{76}Br , ^{86}Y , ^{89}Zr , and ^{124}I . Measurements were conducted for 2 mL microcentrifuge tubes and 10 cc syringes to provide results for two vessels that are commonly placed in dose calibrators to measure activity for either radiochemistry lab work or for *in vivo* injections, respectively. In many cases, our results were significantly different from the calibration setting numbers recommended by the manufacturer. As the CRC-15R and CRC-25R models of dose calibrators from Capintec were used, our results can be used directly for that family of models, including: 15R, 15W, 25R, 25W, 127R, and Ultra-R (Capintec, 2009). However, since the calibrations settings recommended by the manufacturer are interpolated results based on measurements using a different source geometry than what is commonly used in practice for clinical and pre-clinical radiochemistry. Since our results show significant effects of sample geometry, we join with a body of literature to recommend performing in-house calibration for any radionuclide or vessel geometry by utilizing a high-precision measurement, such as HPGe gamma spectroscopy, as a reference for cross-calibration.

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263 References

264 Arras, K.O., 1998. An Introduction To Error Propagation: Derivation, Meaning and Examples of Equation $C_y =$
265 $F_x C_x F_x T$. Technical Report EPFL-ASL-TR-98-01 R3. Swiss Federal Institute of Technology Lausanne,
266 Lausanne, Switzerland, p. 6.

- 267 Avila-Rodriguez, M.A., Nye, J.A., Nickles, R.J., 2008. Production and separation of non-carrier-added ^{86}Y from
268 enriched ^{86}Sr targets. *Appl. Radiat. Isot.* 66, 9-13.
- 269 Beattie, B.J., Pentlow, K.S., O'Donoghue, J., Humm, J.L., 2014. A Recommendation for Revised Dose Calibrator
270 Measurement Procedures for ^{89}Zr and ^{124}I . *PLOS ONE*. 9, e106868.
- 271 Canberra. Detector specification and performance data. Detector model: GC2018, Detector serial No.: 10475. Doc.
272 No.: DPF-009, Rev. H, Date: 2012.
- 273 Canberra. Detector specifications and performance data. Model: GC1818, Serial No.: 2953512. No additional
274 identifying information available.
- 275 Capintec, 2007. CRC-15R: Owner's Manual. Manual No. 9250-0038, Rev. Y.
- 276 Capintec, 2009. Letter sent to customers regarding a new recommendation for calibration setting number for F-18 in
277 select models of dose calibrators.
- 278 Capintec, 2015. CRC-25R: Owner's Manual. Manual No. 9250-0122, Rev. H.
- 279 Ceccatelli, A., Benassi, M., D'Andrea, M., De Felice, P., Fazio, A., Nocentini, S., Strigari, L., 2007. Experimental
280 determination of calibration settings of a commercially available radionuclide calibrator for various clinical
281 measurement geometries and radionuclides. *Appl. Radiat. Isot.* 65, 120-125.
- 282 Cessna, J.T., Schultz, M.K., Leslie, T., Bores, N., 2008. Radionuclide calibrator measurements of ^{18}F in a 3 ml
283 plastic syringe. *Appl. Radiat. Isot.* 66, 988-993.
- 284 Chandra, R., 2011. *Nuclear Medicine Physics: The Basics*, 7th ed. ed. Lippincott Williams & Wilkins, Wolters
285 Kluwer, Philadelphia.
- 286 Coursey, B.M., Calhoun, J.M., Cessna, J.T., 1993. Radioassays of yttrium-90 used in nuclear medicine. *Nucl. Med.*
287 *Biol.* 20, 693-699.
- 288 Croarkin, C., Measurement Process Characterization, in: Croarkin, C., Tobias, P. (Eds.), *NIST/SEMATECH e-*
289 *Handbook of Statistical Methods*. NIST/SEMATECH, Online only.
290 <http://www.itl.nist.gov/div898/handbook/mpc/section5/mpc55.htm>.
- 291 Holland, J.P., Sheh, Y., Lewis, J.S., 2009. Standardized methods for the production of high specific-activity
292 zirconium-89. *Nucl. Med. Biol.* 36, 729-739.
- 293 Ikotun, O.F., Lapi, S.E., 2011. The rise of metal radionuclides in medical imaging: copper-64, zirconium-89 and
294 yttrium-86. *Future Med. Chem.* 3, 599-621.
- 295 International Atomic energy Agency (IAEA)/Division of Life Sciences/Medical Applications Section, 1984. *Quality*
296 *Control of Nuclear Medicine Instruments*. IAEA-TECDOC-317, Vienna.
- 297 Knust, E.J., Dutschka, K., Weinreich, R., 2000. Preparation of ^{124}I solutions after thermodistillation of irradiated
298 $^{124}\text{TeO}_2$ targets. *Appl. Radiat. Isot.* 52, 181-184.
- 299 Ku, H.H., 1966. Notes on the Use of Propagation of Error Formulas. *J. Res. Natl. Bur. Stand. C: Engr. Instr.* 70C,
300 263-273.
- 301 Kume, M., Carey, P.C., Gaehle, G., Madrid, E., Voller, T., Margenau, W., Welch, M.J., Lapi, S.E., 2012. A semi-
302 automated system for the routine production of copper-64. *Appl. Radiat. Isot.* 70, 1803-1806.
- 303 McCarthy, D.W., Shefer, R.E., Klinkowstein, R.E., Bass, L.A., Margeneau, W.H., Cutler, C.S., Anderson, C.J.,
304 Welch, M.J., 1997. Efficient production of high specific activity ^{64}Cu using a biomedical cyclotron. *Nucl.*
305 *Med. Biol.* 24, 35-43.

- McCarthy, T.J., Laforest, R., Downer, J.B., Lo, A.-R., Margenau, W.H., Hughey, B., Shefer, R.E., Klinkowskein, R.E., Welch, M.J., 1999. Investigation of I-124, Br-76, and Br-77 production using a small biomedical cyclotron-can induction furnaces help in the preparation and separation of targets?, in: McCarthy, T.J. (Ed.), 8th Workshop on Targetry & Target Chemistry, Saint Louis, Missouri, United States, pp. 127-130.
- Meijs, W.E., Herscheid, J.D.M., Haisma, H.J., Wijbrandts, R., van Langevelde, F., Vanleuffen, P.J., Mooy, R., Pinedo, H.M., 1994. Production of Highly Pure No-Carrier Added ^{89}Zr for the Labeling of Antibodies with a Positron Emitter. *Appl. Radiat. Isot.* 45, 1143-1147.
- Mo, L., Reinhard, M.I., Davies, J.B., Alexiev, D., Baldock, C., 2006. Calibration of the Capintec CRC-712M dose calibrator for ^{18}F . *Appl. Radiat. Isot.* 64, 485-489.
- National Institute of Standards and Technology (NIST), 2011. Ampoule Specifications and Opening Procedure. Online. <http://www.nist.gov/pml/div682/grp04/srm.cfm>.
- Nayak, T.K., Brechbiel, M.W., 2009. Radioimmunoimaging with longer-lived positron-emitting radionuclides: potentials and challenges. *Bioconjug. Chem.* 20, 825-841.
- Sheh, Y., Kozirowski, J., Balatoni, J., Lom, C., Dahl, J., Finn, R., 2000. Low energy cyclotron production and chemical separation of "no carrier added" iodine-124 from a reusable, enriched tellurium-124 dioxide/aluminum oxide solid solution target. *Radiochim. Acta* 88, 169-173.
- Smith, D.S., Stabin, M.G., 2012. Exposure rate constants and lead shielding values for over 1,100 radionuclides. *Health Phys.* 102, 271-291.
- Tolmachev, V., Lovqvist, A., Einarsson, L., Schultz, J., Lundqvist, H., 1998. Production of Br-76 by a low-energy cyclotron. *Appl. Radiat. Isot.* 49, 1537-1540.
- Tyler, D.K., Woods, M.J., 2002. Syringe Calibration Factors and Volume Correction Factors for the NPL Secondary Standard Radionuclide Calibrator. NPL Report CIRM 56, National Physical Laboratory, Teddington, Middlesex, UK.
- Tyler, D.K., Woods, M.J., 2003. Syringe calibration factors for the NPL Secondary Standard Radionuclide Calibrator for selected medical radionuclides. *Appl. Radiat. Isot.* 59, 367-372.
- Wadas, T.J., Wong, E.H., Weisman, G.R., Anderson, C.J., 2010. Coordinating radiometals of copper, gallium, indium, yttrium, and zirconium for PET and SPECT imaging of disease. *Chem. Rev.* 110, 2858-2902.
- Wooten, A.L., Lewis, B.C., Lapi, S.E., 2015. Cross-sections for (p,x) reactions on natural chromium for the production of ^{52}Mn , ^{54}Mn radioisotopes. *Appl. Radiat. Isot.* 96, 154-161.
- Wooten, A.L., Schweitzer, G.D., Lawrence, L.A., Madrid, E., Lapi, S.E., 2012. An Automated System for Production of ^{89}Zr . *AIP Conf. Proc.* 1509, 201-205.
- Yoo, J., Tang, L., Perkins, T.A., Rowland, D.J., Laforest, R., Lewis, J.S., Welch, M.J., 2005. Preparation of high specific activity ^{86}Y using a small biomedical cyclotron. *Nucl. Med. Biol.* 32, 891-897.
- Zimmerman, B.E., Cessna, J.T., 2000. Experimental determinations of commercial 'dose calibrator' settings for nuclides used in nuclear medicine. *Appl. Radiat. Isot.* 52, 615-619.
- Zimmerman, B.E., Cessna, J.T., Dorton, J.A., 2002. Experimental investigation of dose calibrator response for ^{125}I brachytherapy solutions contained in 5 mL plastic syringes and 2 mL conical glass v-vials as a function of filling mass. *Med. Phys.* 29, 1547-1555.
- Zimmerman, B.E., Cessna, J.T., Unterweger, M.P., Li, A.N., Whiting, J.S., Knapp, F.F., Jr., 1999. A new experimental determination of the dose calibrator setting for ^{188}Re . *J. Nucl. Med.* 40, 1508-1516.

- 346 Zimmerman, B.E., Kubicek, G.J., Cessna, J.T., Plascjak, P.S., Eckelman, W.C., 2001. Radioassays and experimental
347 evaluation of dose calibrator settings for ^{18}F . *Appl. Radiat. Isot.* 54, 113-122.

348 **List of Figures**

349 Fig. 1. **Plots of normalized readout activity ($A_{RO,norm}$) versus calibration setting numbers (N_A)**
350 **over large ranges of settings.** Readout activity was normalized to the largest value that was
351 measured using the calibration setting numbers in that experiment for that radionuclide. Over large
352 ranges for three isotopes with very different total gamma-ray dose rates: ^{52}Mn , ^{64}Cu , and ^{124}I . All
353 results in this figure were from samples in 2 mL microcentrifuge tubes.

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355 **Table 1. Summary of isotope production methods that were used or adapted for the isotopes**
356 **used in this work.**

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Table 1

Product	Target		Isolation Method	Reference(s)
Isotope	Isotope	Material		
^{52}Mn	^{52}Cr (83.7%)	$^{\text{nat}}\text{Cr}$ metal foil	(No isolation performed—only digestion of Cr target by HCl.)	-
^{64}Cu	^{64}Ni (0.9%)	Electroplated ^{64}Cu metal	Anion-exchange chromatography	<u>AM</u> : (Kume et al., 2012) <u>SC</u> : (McCarthy et al., 1997)
^{76}Br	^{76}Se (9.4%)	Pressed $^{76}\text{Cu}_2\text{Se}$ pellet	Dry distillation followed by thermal chromatography	<u>AM</u> : Not yet published. <u>SC</u> : (McCarthy et al., 1999) (Tolmachev et al., 1998)
^{86}Y	^{86}Sr (9.9%)	Pressed ^{86}SrO pellet	pH-based precipitation followed by filtration	<u>AM</u> : Not yet published. <u>SC</u> : (Avila-Rodriguez et al., 2008) (Yoo et al., 2005)
^{89}Zr	^{89}Y (100%)	$^{\text{nat}}\text{Y}$ metal foil	Hydroxamate resin chromatography	<u>AM</u> : (Wooten et al., 2012) <u>SC</u> : (Holland et al., 2009) (Meijs et al., 1994)
$^{124}\text{I}^\dagger$	^{124}Te (4.7%)	$\text{TeO}_2/\text{Al}_2\text{O}_3$	Dry distillation	<u>SC</u> : (Knust et al., 2000) (Sheh et al., 2000)

All isotopes were produced via (*p,n*) reactions. † Purchased from 3D Imaging (Maumelle, Arkansas, United States). All other isotopes were produced in-house at WUSM/MIR. AM: automated module; SC: separation chemistry.

Table 2	
Well Diameter	6.1 cm
Well Depth	25.4 cm
Electrometer Accuracy	Better than $\pm 2\%$
System Precision	Better than $\pm 0.1\%$ FSD
System Linearity	Within $\pm 2\%$
Equation for recommended calibration numbers	$N_A = 1076*(R_A - 0.080)$
N_A =Calibration number; R_A =the response of the detector to Isotope A.	
Source: (Capintec, 2007, 2015).	

Table 3

Isotope	Gamma Factor [†]	From Manual [‡]	New Calibration Setting		Percent Difference in Activity Readout (%)
	Γ (R·cm ² /mCi·h)		2 mL Tube	10 cc Syringe	
⁵² Mn	18.4	676÷2	759±12 (÷2)	777±13 (÷2)	+10.2%
⁶⁴ Cu	1.05	15 or	16±2	108±2 (x2)	-3.6% [*]
		115 (x2)			
⁷⁶ Br	14	495÷2	604±9 (÷2)	800±9 (÷2)	+52.6%
⁸⁶ Y	18.9	711÷2	762±12 (÷2)	815±9	-44.1%
⁸⁹ Zr	6.59	465	514±6	527±6	+11.2%
¹²⁴ I	6.59	570	29±1	733±7	+24.6%

For (x2) or (÷2), the activity readout from the dose calibrator should be multiplied or divided by 2 to obtain the correct activity measurement. [†]Gamma factor describes the dose rate from gamma radiation emitted by an isotope. (Gamma factor data from: (Smith and Stabin, 2012)) [‡]All recommended dial settings were the same in the manuals for both the CRC-15R and CRC-25R models, except for ⁷⁶Br and ⁸⁹Zr, which were only listed in the manual for the CRC-15R. (Capintec, 2007, 2015). ^{*}Calculated relative to the activity readout using the 15 calibration setting number.

Table 4

Isotope	Reference	Method	Capintec Model ¹	Vessel Geometry	Source		Result	
					Vessel Volume V_{vessel} (mL)	Liquid Volume V_{source} (mL)	Setting Number ² N_A (-)	Readout Difference ³ (%)
¹⁸ F	(Cessna et al., 2008)	4 π β -LS	CRC-15R	NIST ampoule	5	5	472	+6.4
		"	CRC-15R	Syringe	3	1	484	+8.9
		"	CRC-15PET	"	"	"	501	+12.7
		"	CRC-12	"	"	"	500	+13.3
	(Mo et al., 2006)	4 π β -LS	CRC-712M	Wheaton vial	-	-	459	-
	(Zimmerman et al., 2001)	HPGe	CRC-12	Monojet syringe	12	9	482	+8.3
		"	CRC-35R	NIST ampoule	-	-	477	+6.2
	(Zimmerman and Cessna, 2000)	4 π β -LS	CRC-12	Mallinckrodt dose vial	10	5	463	+4.5
		"	CRC-12	plastic syringe	12	9	482	+7.3
⁸⁹ Zr	(Beattie et al., 2014)	HPGe	CRC-15R	borosilicate glass vial	20	10	517	+8.00-12.0
⁹⁰ Y	(Coursey et al., 1993)	HPGe	CRC-12	NIST ampoule	-	-	48 ($\times 10$)	+50
¹²⁴ I		HPGe	CRC-15R	borosilicate glass vial	20	10	494 (with Cu filter)	+14.9-28.0
¹²⁵ I	(Zimmerman et al., 2002)	NaI(Tl)	CRC-12	plastic syringe	5	-	497	+45
		"	CRC-12	conical glass dose vial	2	-	143	-42
¹³³ Xe	(Zimmerman and Cessna, 2000)	4 π β -LS	CRC-12	Dupont dose vial	3	-	181	-2.7
		"	CRC-12	NIST ampoule	-	-	184	-1.7
¹⁸⁸ Re	(Zimmerman and Cessna, 2000)	4 π β -LS	CRC-12	SoloPak dose vial	5	-	620 ($\times 10$)	+22.2
	(Zimmerman et al., 1999)	4 π β -LS	CRC-12	NIST ampoule	-	-	630 ($\times 10$)	+30

¹All dose calibrator models were by Capintec. These results for calibration setting numbers may translate across certain models of Capintec dose calibrators, but not necessarily all models. ²Some calibration setting numbers require that the activity readout be multiply or divided by a factor for an accurate measurement. ³This column is the percentage difference of the activity readout using the calibration number from the user manual versus the activity readout using the experimentally determined calibration number.

Figure 1