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Original paper

A comparison of four radionuclide dose calibrators using various radionuclides and measurement geometries clinically used in nuclear medicine

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ABSTRACT

Purpose: Reliable quantification of radioactivity in nuclear medicine is becoming increasingly important in various therapeutic applications requiring a high accuracy of nuclear medicine measuring equipment, such as radionuclide calibrators. In this study the accuracy of four different radionuclide calibrators was assessed for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F for measurement geometries clinically used.

Methods: Syringes and vials were prepared with a reference activity using a stock solution of which the activity concentration was determined using gamma-ray spectroscopy. The accuracy of four different radionuclide calibrator systems, ISOMED 2000, ISOMED 2010, VIK-202 and Capintec CRC-25R, was assessed by comparing the measured activity to the reference activity.

Results: Deviations in measured activity from reference values were found up to 12.5%, 32.0%, 29.0% and 12.6% for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F, respectively. For ^{68}Ga all radionuclide calibrators systematically overestimated the activity by 10–20%. For ^{111}In, large differences in activity measurements were observed between different source geometries, in particular between syringes and vials. Deviations between radionuclide calibrator systems were found up to 11.8%, 44.4%, 14.4% and 8.7% for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F, respectively. When comparing similar syringe types of different brands filled with identical stock solution volume, deviations up to 1.8%, 5.8%, 10.2% and 3.2% were found for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F.

Conclusion: Substantial deviations in measured activity were found for all radionuclides and radionuclide calibrators, which may result in erroneous activity dosing and image quantification. This underlines the importance of thorough validation of radionuclide calibrators for all measurement geometries and radionuclides clinically used.

1. Introduction

In nuclear medicine, absolute quantification of radioactivity is becoming increasingly important for the application of personalized dosimetry, therapy response monitoring and the development of new imaging biomarkers [1–4]. To achieve reliable image quantification of activity, accurate assessment of the amount of activity administered, is crucial. The latter is also required for legislational reasons [5]. According to (inter)national guidelines, each unit dose of radiopharmaceuticals to be administered to a patient should be measured using a radionuclide calibrator consisting of a well-type ionization chamber [6–8] with a minimum accuracy of 5 to 10% for all radionuclides and sample geometries used in clinical practice [6–10].

Radionuclide calibrators, commonly marketed as medical devices, are available from different manufacturers in many different models, depending on the intended use such as the type and amount of radioactivity of the radionuclides to be measured. Because of their medical device status, high costs, expertise and time investment needed for on-site calibration and validation, in practice these devices are often implemented without thorough on-site validation. When on-site validation is performed, it is often limited to a comparison to other available radionuclide calibrators for few radionuclides and sample geometries,

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as reference standards from certified suppliers are expensive and alternative well-calibrated radioactivity measurement equipment is not available in the vast majority of centers.

Re-entrant ionization chambers consist of a gas filled chamber coupled to a high voltage supply. Ionizing radiation, emitted from a radioactive sample introduced inside the chamber, causes ionization of the gas molecules resulting in an electrical current which is amplified and measured. The amount of electrical current is proportional to the activity of the sample. Consequently, the measured current can be converted to an activity value using a radionuclide specific calibration factor, sometimes called the dial setting. Typically, calibration factors of commonly used radionuclides are already provided by the manufacturer. In general, these calibration factors are determined either by direct measurement of radioactive samples having a traceability chain to a primary standard [11] or by calculation using an energy dependent sensitivity curve [12]. In both cases, the provided calibration factors are often only validated for specific types of vials or syringes, usually specified by the manufacturer. However, as measurements with a radionuclide calibrator are susceptible to geometrical influences (for instance the position of the sample in the chamber and sample volume) and container type (wall thickness and wall material), care has to be taken when different types of vials or syringes are used. This is particularly true for radionuclides emitting beta radiation or low-energy X-ray or gamma photons as for this type of ionizing radiation a substantial amount of self-absorption can occur [13,14].

In a recent study, Saldarriaga Vargas et al. [15] performed an intercomparison among 15 Belgian hospitals and 38 radionuclide calibrators for both a 10 mL glass vial and 10 mL plastic syringe for ^{99m}Tc, ^{18}F and ^{111}In, three commonly used radionuclides in nuclear medicine. In their study, numerous deviations in measured from true activity values larger than 10% and up to 72% were observed, in particular for syringes containing ^{111}In, showing the importance of accurate validation of measurement geometries used in clinical practice.

In this study, the accuracy of four different types of radionuclide calibrators commonly used in nuclear medicine was investigated for four radionuclides widely applied in nuclear medicine imaging (^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F) using a well-calibrated gamma spectroscopy system as a reference. In addition, the influence of sample geometry was assessed using various types of commercially available vials and syringes. Finally, the inter-system accuracy of five radionuclide calibrators of the same type and manufacturer was assessed.

2. Materials and Methods

2.1. Gamma spectroscopy system

A high-purity semiconductor (germanium) gamma-ray spectroscopy system (Canberra HPGe GR1018, Mirion Technologies, Smyrna, Georgia, USA) was fully calibrated for photon energy and efficiency according to the procedures described by the International Atomic Energy Agency (IAEA) [8] using seven calibrated solid point sources. Each point source was encapsulated in a thin plastic disk with a total thickness less than 1 mm. Self-absorption of the point sources was considered negligible. Details on the point source activity values are shown in Table 1.

In order to avoid coincidence sum effects of low energy X-ray photons, 2 mm of copper was placed between the source and detector. Coincidence sum effects of higher energy photons were reduced by positioning the sources at a distance of 18.5 cm from the detector surface. The measurement time was sufficiently long to achieve a minimum net number of counts of $2.5{\cdot}10^3$ for each photon energy. System dead time was below 3% for each measurement. All spectra were corrected for background. For each photon energy, the energy efficiency was determined used the standard software (Genie 2 K) provided by the manufacturer. Finally, the energy efficiency was determined as a function of photon energy using a fifth order polynomial fit in the log–log scale as shown in Fig. 1.

Table 1
Characteristics of point sources used for energy and efficiency calibration of the semiconductor gamma spectroscopy system.

Radionuclide	Activity (kBq)	Activity uncertainty (%)
^{22}Na	$2.21{\cdot}10^1$	3.00
^{57}Co	$1.81{\cdot}10^1$	3.00
^{60}Co	$1.57{\cdot}10^1$	1.90
^{133}Ba	$1.88{\cdot}10^2$	3.00
^{137}Cs	$3.15{\cdot}10^2$	3.00
^{152}Eu	$1.06{\cdot}10^1$	8.7
^{241}Am	$4.26{\cdot}10^2$	3.00

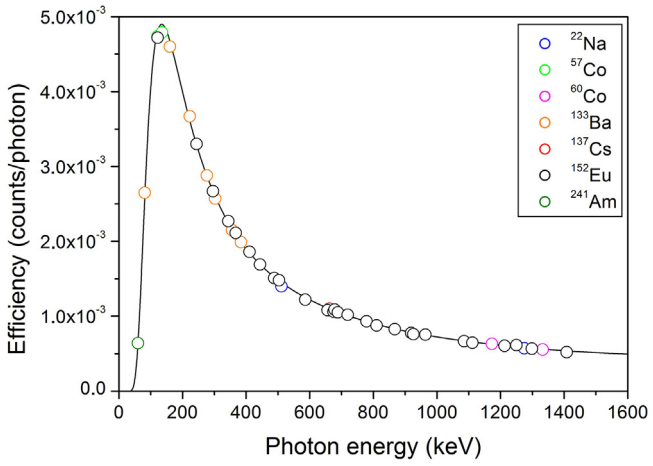

Fig. 1. Measurement efficiency of the gamma spectroscopy system as function of the photon energy. The solid line represents the fitted curve.

2.2. Stock solution preparation

Four different radionuclides commonly used in nuclear imaging were used in this study: [^{99m}Tc]-TcO4$^-$, [^{111}In]-InCl$_3$, [^{18}F]-FDG and [^{68}Ga]-Ga-Dotatate. For each radionuclide a homogeneous stock solution of approximately 2 MBq/mL was prepared in a glass measuring cup. In order to accurately determine the radioactivity concentration of the stock solution, a minimum of three aliquots were prepared from the stock solution by pipetting 10 µL (30 µL for ^{68}Ga) into a 1.5 mL Eppendorf cup (wall thickness approximately 1 mm). The exact amount of radioactive solution was determined gravimetrically by weighing the samples before and after filling using an analytical balance (XS105DU/M, Mettler-Toledo, Tiel, The Netherlands). Each sample was then measured with the gamma spectroscopy system using the same measurement setup (at a detector-to-sample distance of 18.5 cm, using 2 mm of copper between the sample and the detector) as for the efficiency calibration measurements. At this detector-to-sample distance, the difference in geometry efficiency between the 7 point sources used for the efficiency calibration of the spectroscopy system and the 10–30 µL Eppendorf sample was considered to be negligible. In addition, each stock solution was checked for radionuclidic impurities by visual assessment of the measured spectra. For each of the photopeaks shown in Table 2 the net number of counts measured ($> 3.0{\cdot}10^4$ for ^{99m}Tc, ^{111}In and ^{18}F, $> 5.0{\cdot}10^3$ for ^{68}Ga) was determined, corrected for system dead time ($< 5\%$ for ^{99m}Tc, ^{111}In and ^{18}F, less than 10% for ^{68}Ga) and radioactive decay. Although the majority of photons emitted by ^{68}Ga comprise 511 keV annihilation photons, these photons cannot be used for quantitative assessment of the radioactivity concentration of the stock solution due to the large end-point energy (1.90 MeV) of the emitted positrons. This will result in an increased distance traveled by the positron before annihilation, causing the positron annihilation to

Table 2
Photopeaks used for determination of sample activity [16].

Radionuclide	Photon energy (keV)	Photon yield (%)
^{99m}Tc	140.5	89
^{111}In	171.3 & 245.4	90.7 & 94.1
^{18}F	511.0	193
^{68}Ga	1077.3	3.2

occur outside the sample, decreasing the geometric efficiency of the measurement. Therefore, the 1077.3 keV photon peak is used instead. For each sample, the activity was calculated using the measurement efficiency of the gamma spectroscopy system and the photon yield (for ^{111}In the average activity determined from both photopeaks was taken, see Table 2). Finally, the radioactivity concentration (MBq/g) of each stock solution was determined as the average radioactivity concentration of the three samples calculated by dividing the sample activity by the sample weight.

An uncertainty analysis was performed to assess the measurement uncertainty (Δ) in the stock solution radioactivity concentration (a) determination. In this analysis, the statistical variation in measured number of counts (N), deviations in efficiency curve fitting (ε) and measurement uncertainty of the sample weight (m) were considered to be contributing factors to the total measurement uncertainty. The total percentage measurement uncertainty can be determined according to

$$\Delta a(\%) = \frac{\Delta a}{a} \times 100\% = \sqrt{\left(\left(\frac{\Delta N}{N}\right)^2 + \left(\frac{\Delta \varepsilon}{\varepsilon}\right)^2 + \left(\frac{\Delta m}{m}\right)^2\right)} \times 100\% \quad (1)$$

For the percentage measurement uncertainty of ^{111}In both measured photon peaks (171.3 keV and 245.4 keV) were taken into consideration.

2.3. Syringe and vial preparation

For all radionuclides, the influence of syringe and vial type on the radionuclide dose calibrator accuracy was investigated for a variety of commercially available syringes and vials used in clinical practice. An overview of all syringe and vial types used in this study is shown in Table 3.

Syringes and vials were all prepared from the stock solution. The total amount of radioactive solution was determined gravimetrically by weighing the syringes and vials before and after filling using an analytical balance (XS105DU/M, Mettler-Toledo, Tiel, The Netherlands). In order to avoid measurement interference caused by residual radioactivity present in the needle, all syringes were fitted with a clean needle (B. Braun, 29G 45 mm) after filling. For each syringe/vial, the exact amount of radioactivity, defined as the reference activity, was determined by multiplication of the net mass of solution present in the syringe/vial, which was determined using the clean needle, with the radioactivity concentration of the stock solution determined from the gamma spectroscopy measurements. The amount of activity was always > 1 MBq, as per manufacturers guidelines.

2.4. Radionuclide calibrator systems

The accuracy of four different radionuclide calibrator systems was assessed: ISOMED 2000 (MED Nuclear Medizintechnik, Dresden, Germany), ISOMED 2010 (MED Nuclear Medizintechnik, Dresden, Germany), VIK-202 (Comecer Netherlands, Joure, The Netherlands) and Capintec CRC-25R (Capintec Inc., Florham Park, New Jersey, USA). For all radionuclide calibrators the standard factory set calibration factors were applied and standard sample holders were used, without any posthoc modification to the data (for example, the software package IBC (Comecer) was not used). Each radionuclide calibrator was calibrated as prescribed by the manufacturer using a ^{137}Cs source. All radionuclide calibrators were synchronized to the same time.

2.5. Radionuclide calibrator accuracy measurements

The accuracy of the radionuclide calibrator systems was assessed by comparing the measured activity in the syringes and vials to the reference activity, based on the gamma spectroscopy measurements.

In the first part of this study (study I), for each type of radionuclide calibrator the measurement accuracy was determined for all four radionuclides for different types of syringes and vials used for daily patient care in our institution, shown in parentheses in Table 3. For each type of syringe/vial various amounts of solution were used as shown in Table 4.

2.6. Effect of syringe geometry

In the second part of the study (study II), the measurement accuracy of the ISOMED 2010 radionuclide calibrator was assessed for three different manufacturers of syringes, as shown in parentheses in Table 3, to study the effect of syringe type on measurement accuracy. For each syringe both a minimum solution volume of 0.5 mL and the maximum solution volume corresponding to each syringe type were investigated.

2.7. Radionuclide calibrator inter-system variation

Finally, in the third part of the study (study III), the inter-system

Table 3
Overview of all syringe and vial types. The numbering in parentheses shows which syringes/vials were used in which part of the study.

Manufacturer	Syringe/vial types	Calibrator measurement uncertainty (I)	Effect of syringe type on measurement accuracy (II)	Inter-system measurement accuracy ISOMED 2010 (III)
B. Braun Medical	1 mL luer slip		X	
	3 mL luer lock	X	X	X
	5 mL luer lock	X	X	X
	10 mL luer lock		X	
Becton Dickinson (BD)	1 mL luer slip		X	
	1 mL luer lock	X	X	X
	2.5 mL luer slip		X	
	5 mL luer slip		X	
	10 mL luer slip		X	
Terumo	1 mL luer slip		X	
	3 mL luer lock		X	
	5 mL luer lock		X	
	10 mL luer lock		X	
Alltech	2 mL vial	X		
Mallinckrodt	10 mL vial	X		X

Table 4
Overview of solution volumes for determination of calibrator accuracy used in the first part of the study (study I).

Syringe/vial type	Solution volume (mL)
1 mL syringe	0.5, 1.0
3 mL syringe	0.5, 1.0, 2.0, 3.0
5 mL syringe	0.5, 1.0, 2.0, 3.0 5.0
2 mL vial	0.5, 1.0, 2.0
10 mL vial	0.5, 1.0, 2.0, 3.0, 5.0, 10.0

variation of five ISOMED 2010 radionuclide calibrator systems, manufactured between 2012 and 2016, was investigated for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F for syringes and vials used in clinical practice. The inter-system variation was defined as the standard deviation of the measurements between the five systems divided by the average measurement value multiplied by 100%. For each syringe both a minimum stock solution volume of 1.0 mL (0.5 mL for the 1.0 mL syringe) and the maximum solution volume corresponding to each syringe type were studied. In addition, the inter-system variation was assessed for a 10 mL vial filled with 3.0 mL of stock solution volume.

3. Results

3.1. Stock solution

For all radionuclides, no radionuclidic impurities were identified by visual assessment of the acquired gamma spectroscopy spectra. The average percentage deviation in the efficiency curve fitting with respect to the measured efficiency values was 1.3% (maximum deviation 3.6%), indicating a good agreement between the fitted efficiency curve and the measured efficiency values over the complete energy range. With a statistical variation in total number of collected counts of 0.33% (0.82% for ^{68}Ga) and a sample mass uncertainty of 1.4% (0.5% for ^{68}Ga), the total measurement uncertainty of the stock solution activity concentration was 2.0% for ^{99m}Tc and ^{18}F, 1.4% for ^{111}In and 1.6% for ^{68}Ga, calculated according to Eq. (1).

3.2. Radionuclide calibrator accuracy measurements

In Fig. 2 the percentage deviation of radioactivity measured versus the reference activity value is shown, for each type of radionuclide calibrator and each syringe/vial approximately half filled with stock solution. Detailed information of all filling volumes of the samples can be found in Appendix A.

In Fig. 2 it can be seen that in the majority of the scenarios deviations exceed the 5% limit recommended in several (inter)national guidelines [7,8] for all radionuclides. For each radionuclide deviations exceeded even the 10% limit, which is the generally accepted accuracy limit for diagnostic purposes [9,10], for one or more sample geometries for at least one radionuclide calibrator system. Maximum deviations found with respect to the reference activity value, were 12.5%, 32.0%, 29.0% and 12.6% for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F, respectively. Interestingly, for ^{68}Ga all radionuclide calibrators systematically overestimated the activity, typically by 10–20%. For ^{111}In, large differences in activity measurements were observed when comparing both source geometry, in particular between syringes and vials, and radionuclide calibrator systems. Deviations between radionuclide calibrator systems found were up to 11.8%, 44.4%, 14.4% and 8.7% for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F, respectively.

3.3. Effect of syringe geometry

In Fig. 3 the percentage deviations of measured activity versus the reference activity value for different types of syringes with maximum amount of stock solution measured with the ISOMED 2010 radionuclide calibrator are shown. Detailed information of all filling volumes can be found in Appendix B. When comparing similar syringe types of different brands filled with identical stock solution volume, deviations up to 1.8%, 5.8%, 10.2% and 3.2% were found for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F.

3.4. Radionuclide calibrator inter-system variation

In Fig. 4 the inter-system variation determined for five ISOMED 2010 radionuclide calibrator systems for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F for syringes filled with maximum amount and vials filled with 3–4 mL of stock solution is shown. Detailed information of all filling volumes can be found in Appendix C. The maximum inter-system variation was 1.1%, 1.6%, 2.6% and 2.0% for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F, respectively. Furthermore, the maximum deviation between two radionuclide calibrator systems was 2.6%, 3.9%, 6.4% and 5.1% for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F, respectively. These results show a good reproducibility in measurement value between different radionuclide calibrator systems of the same manufacturer and type.

4. Discussion

4.1. Radionuclide calibrator measurement accuracy validation

Validation of measurement accuracy of radionuclide calibrators for all clinically used radionuclides and measurement geometries (syringes/vials, filling volume) is recommended in various (inter)national guidelines [6–10]. However, in practice radionuclide calibrators are often implemented without thorough on-site validation as a result of the medical device status of radionuclide calibrator systems combined with the high costs, required expertise and time investment needed for this validation. In a recent study investigating the radionuclide calibrator measurement accuracy for ^{99m}Tc, ^{111}In and ^{18}F, among 15 Belgian medical centers, it was reported that none of the participating centers assessed the measurement accuracy for short-lived radionuclides used in clinical practice [15]. Although the majority of radionuclide calibrator systems determined the activity correctly within 10% for ^{99m}Tc and ^{18}F, large deviations exceeding this 10% limit (up to 72%) were observed for ^{111}In, stressing the importance of proper validation of radionuclide calibrator measurement accuracy for all radionuclides and measurement geometries.

4.2. Measurement accuracy of ^{99m}Tc, ^{18}F, ^{111}In and ^{68}Ga

For all radionuclide calibrators and all radionuclides investigated in this study, deviations in the measured activity with respect to the reference activity were observed that exceeded the 5% accuracy limit as recommended in (inter)national guidelines [7,8]. In clinical practice, this will have a negative effect on patient activity dosing and absolute image quantification, which is crucial in for instance radiation dosimetry applications or therapy response monitoring.

4.2.1. ^{99m}Tc

For ^{99m}Tc the deviations were smaller than 10% for the majority of syringes/vials for all radionuclide calibrator systems with a maximum deviation of 12.5%. Although these measurements are in agreement with accuracy values reported for ^{99m}Tc in literature [13,15,17], we observed a systematic underestimation of the ^{99m}Tc activity for all radionuclide calibrators, which may partly be explained by the measurement uncertainty in the stock solution activity concentration of 2.0%.

4.2.2. ^{18}F

For ^{18}F the deviations were smaller than 10% for the majority of syringes/vials for all radionuclide calibrator systems with a maximum deviation of 12.6%. In a recent study, Saldarriaga Vargas et al. also found that the accuracy of most radionuclide calibrator systems was

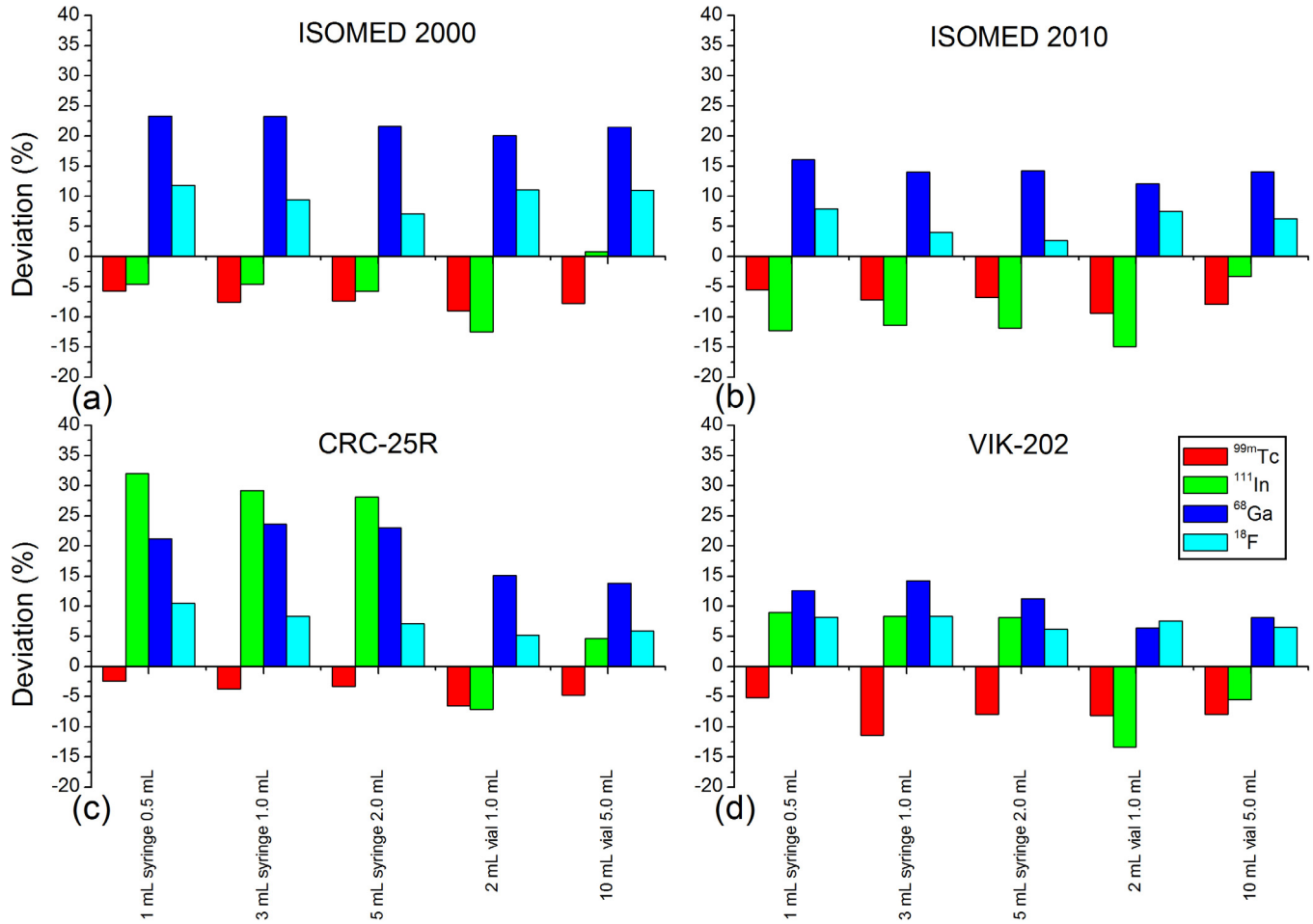

Fig. 2. Percentage deviation of measured activity versus reference activity value of ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F for each type of radionuclide calibrator: (a) ISOMED 2000, (b) ISOMED 2010, (c) CRC-25R, (d) VIK-202.

better than 10% for ^{18}F [15]. However, in contrast to their study, our results show a systematic overestimation in the measured activity value for all radionuclide calibrator systems in agreement with previous studies reported in literature [13,18,19]. Part of this systematic overestimation may be explained by the measurement uncertainty in the stock solution activity concentration of 2.0%.

4.2.3. ^{111}In

For all radionuclide calibrators the measurement deviations were smaller than 10% for the 10 mL glass vial. In contrast, with the exception of the ISOMED 2000 radionuclide system, deviations larger than 10% were observed for the syringe measurements with a maximum deviation of 32.0%, in agreement with previous studies reported in literature [15,17,20]. This discrepancy is caused by the high number of low-energy X-ray photons (energy: 23 keV, yield: 69.4%; energy: 26 keV, yield: 13.4% [16]) emitted by ^{111}In, which are more likely to be absorbed by the glass vial than in the plastic syringes. Using Monte Carlo simulations, Olsovcová showed that the radionuclide calibrator response at 30 keV is approximately two times higher for a plastic syringe compared to a glass vial [21]. Since radionuclide calibrators are typically calibrated using glass vial samples traceable to primary or secondary standards (either by direct measurement or determination of the radionuclide calibrator response curve as a function of photon energy) large deviations in measurement accuracy are observed when no geometry correction factor for syringes is applied, as is the case for the Capintec radionuclide calibrator system. Although the ISOMED 2000 and ISOMED 2010 systems both apply container- and filling volume specific calibration factors for all radionuclides, the ISOMED 2010 system shows substantial larger deviations (> 10%) for the syringes compared to the ISOMED 2000 system. After reporting these deviations to the manufacturer (MED), our results were confirmed upon which the manufacturer adjusted our syringe calibration factors of ^{111}In by 7–14 %. The large discrepancy between vial- and syringe measurements when using the VIK-202 can be corrected to some degree by a post-hoc data modification by the IBC software package.

4.2.4. ^{68}Ga

For ^{68}Ga, all radionuclide calibrator systems showed a large and systematic overestimation in measured activity of the order of 10–25%. Similar deviations in the measurement accuracy of ^{68}Ga were recently reported in an Australian multi-center trial for a variety of Capintec radionuclide calibrator systems [22]. Since we were able to verify our findings using quantitative positron emission tomography (PET) measurements (data not shown) we reported these deviations to the manufacturer (MED) upon which the manufacturer confirmed our findings and changed their ^{68}Ga calibration factors for the ISOMED 2010 system by approximately 12%.

4.3. Comparison between different radionuclide calibrator systems

Our study showed very good agreement between five different ISOMED 2010 radionuclide calibrators with maximum inter-system variations of 1.1%, 1.6%, 2.6 and 2.0% for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F, respectively. However, among different types of radionuclide calibrator systems large deviations were found up to 11.8%, 44.4%, 14.4% and 8.7% for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F, respectively. These deviations can

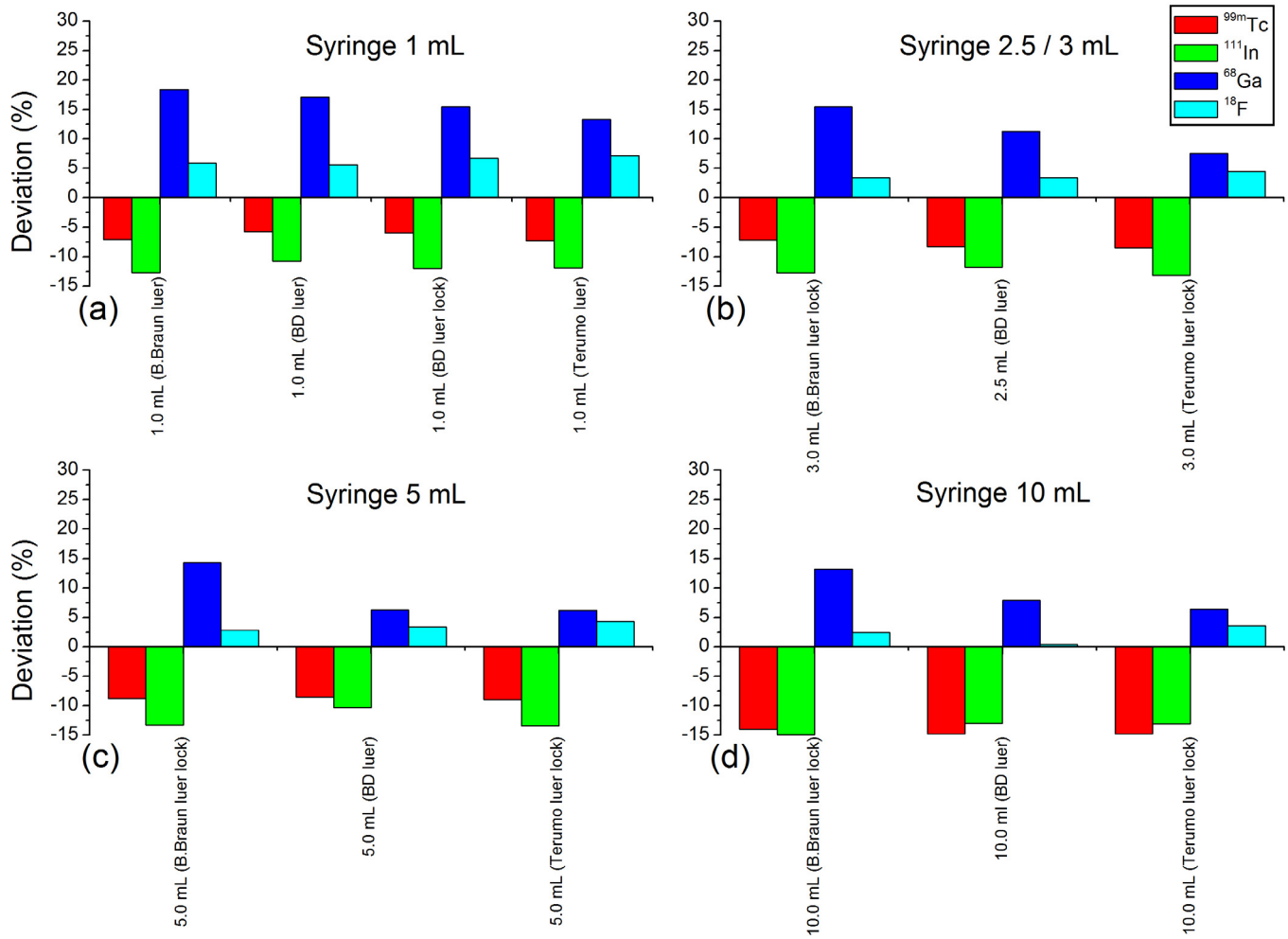

Fig. 3. Percentage deviation of measured activity versus reference activity value of ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F for different types of syringes (1 mL, 2.5/3 mL, 5 mL, 10 mL, see Table 3) measured with the ISOMED 2010 radionuclide calibrator.

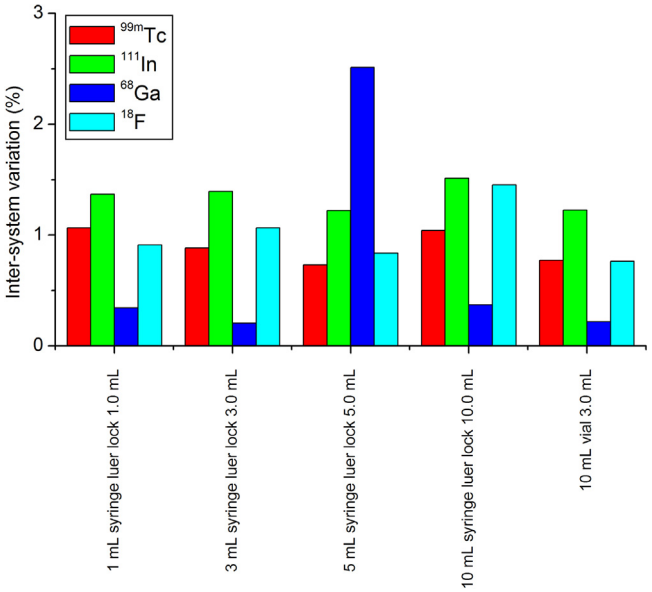

Fig. 4. Inter-system variation of five ISOMED 2010 radionuclide calibrator system measured for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F.

in part be explained by the fact that different manufacturers adopt a different implementation of their calibration factors. Whereas the ISOMED 2000 and 2010 radionuclide calibrators have calibration factors for each container type for a variety of filling volumes for each radionuclide, the Capintec CRC-25R system only allows for one calibration factor per radionuclide (albeit that the anticipated syringe corrections are tabulated in the Capintec owner's manual [12]). The VIK-202 system uses a single calibration factor per radionuclide, in combination with a geometric correction factor for syringes that can be applied in the Comecer IBC software package. This correction factor is to be determined by the user.

Although validation of absolute accuracy is in general difficult for medical centers, a relative cross-calibration between different radionuclide calibrator systems can fairly easily be achieved and is, in view of our findings, highly recommended. This is in particular true when different types of radionuclide calibrator systems are in use in one nuclear medicine department. Nevertheless, in clinical practice such cross-calibration is often not conducted as reported in a recent study [15].

4.4. Effect of syringe brand and filling volume

When comparing similar syringe types of different manufacturers filled with identical stock solution volume, deviations up to 1.8%, 5.8%, 10.2% and 3.2% were found for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F. Filling volume only had a minor effect, typically less than 5%. These

findings are similar to the deviations reported by Bochud et al. [20]. However, larger deviations were observed between the syringes and vials, in particular for ^{111}In. This effect is caused by the aforementioned high degree of absorption of low-energy X-rays in the glass vials compared to the plastic syringes. Consequently, the use of sample (or even filling volume) specific calibration factors instead of one single calibration factor per radionuclide is widely advocated in literature, in particular for radionuclides emitting low-energy photons [8,13,20]. Alternatively, it has been shown that the strong dependence of the sample geometry caused by low-energy X-ray photons can be largely eliminated using a copper filter absorbing almost all low-energy X-ray photons before reaching the ionization chamber of the radionuclide calibrator [23]. However, this approach leads to a lower sensitivity and an inherent risk for erroneous measurement when the copper filter is mistakenly not used, and it is also not applicable for radionuclides emitting only low-energy photons such as ^{125}I. Moreover, both methodologies require a manual adjustment of the calibration factors from factory settings which is sometimes not allowed due to the medical device status of radionuclide calibrator systems. Even if this is possible, we strongly recommend to contact the manufacturer of the radionuclide calibrator system prior to manual adjustment of calibration factors.

4.5. Limitations

An important limitation of our study is the fact that our reference activity values are not traceable to a secondary standards radioactivity laboratory (SSRL) or national metrology institute (NMI) as required for the calibration of radionuclide calibrators according to publications of the International Atomic Energy Agency (IAEA) [8,24]. Despite this limitation, the use of gamma-ray spectroscopy with semiconductors is a frequently used and well-established technique in a large number of laboratories [25]. In fact, Koskinas et al. [26] showed that for a well-calibrated gamma-ray spectroscopy system, using a similar setup as in our study, the deviation in measured activity with respect to a secondary standard was smaller than 3% for radionuclides emitting gamma photons having an energy higher than 140 keV, which is comparable to the measurement uncertainty found in our study. Indeed, in our study we found that using gamma-ray spectroscopy we were able to identify errors in the calibration factors for ^{111}In and ^{68}Ga exceeding the 10% limit, which were confirmed by the radionuclide calibrator manufacturer. Therefore, we conclude that even though the use of on-site gamma-ray spectroscopy with semiconductors (meaning not traceable to a SSRL or MNI) is not recommended for calibration of radionuclide calibrator systems, it can be used to assess radionuclide calibrator measurement accuracy.

An important pitfall to consider when using semiconductors for the measurement of small positron emitting sources is the positron range effect [25]. As a result of the distance traveled by the positron before annihilation, the annihilation of the positron and therefore the emission of the two 511 keV annihilation photons can occur outside the radioactive sample, decreasing the geometric efficiency of the measurement. The fraction of positrons annihilating outside the sample increases with increasing end-point energy of the positrons. Having a high positron end-point energy of 1.90 MeV, the stock solution concentration of ^{68}Ga cannot be reliably determined based on the 511 keV photopeak using the described gamma-ray spectroscopy setup, necessitating the use of the 1077.3 keV photopeak instead. However, a combination of a relatively low intrinsic efficiency at this energy (see also Fig. 1), low photon yield of 3.2% and short half-live of 67.7 min, resulted in a substantial decrease in the total number of counts that could be collected for the ^{68}Ga samples compared to the other radionuclides. This resulted in an increase in counting statistics uncertainty which was compensated by using a 3 times larger sample volume. Being a pure positron emitter, for ^{18}F the activity concentration of the stock solution had to be determined using the 511 keV photopeak. Although with a low positron end-point energy of 0.63 MeV, for ^{18}F the positron range effect may have resulted in a small underestimation of the reference activity. To exclude this phenomenon to be the cause of the observed systematical overestimation of the activity measured by the radionuclide calibrators, the positron range effect on the gamma spectroscopy efficiency was investigated (data not shown). This was done by measuring a variety of ^{18}F point sources of different volumes (10 – 50 μL) and placing a thin layer of agarose gel on top of the liquid surface to prevent positrons escaping the sample. As no significant influence on the measurement efficiency was observed, it was concluded that an underestimation in the reference activity values resulting from a positron range effect can be excluded.

5. Conclusion

The measurement accuracy of four different radionuclide calibrators of three different manufacturers was investigated for ^{99m}Tc, ^{111}In, ^{68}Ga and ^{18}F using measurement geometries in clinical conditions. For all radionuclide calibrators and all radionuclides, deviations were found exceeding the limits recommended in (inter)national guidelines for one or more measurement geometry. In clinical practice, this will have a negative effect on patient activity dosing and absolute image quantification.

6. Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2019.03.012.

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