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^{68}Ga activity calibrations for nuclear medicine applications in Cuba.

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ABSTRACT

The realization and dissemination of the ^{68}Ga activity measurement unit in Cuba is presented. Firstly, the implementation of the Triple to Double Coincidence Ratio (TDCR) method is described for the calibration of the activity concentration of a ^{68}Ga solution using a HidexTM commercial liquid scintillation counter and a FORTRAN code developed for the calculation of the ^{68}Ga counting efficiencies in the given measurement system. The relative expanded uncertainty ($k=2$) associated with the ^{68}Ga activity concentration obtained with the TDCR method is equal to 2 %. With the aim to validate this measurement uncertainty estimate, the method is also applied to an Amersham standard solution of ^{22}Na - a positron emitter with a similar decay mode to the ^{68}Ga disintegration scheme from the point of view of type of emitted particles detected in the measurement system. The observed difference between the measured ^{22}Na activity concentration by the TDCR method and the corresponding reference value traceable to NIST is equal to 0.16 %.

Outcomes of transferring the ^{68}Ga activity standard, realized with the TDCR method, to the secondary standard radionuclide calibrator Capintec CRCTM 15R and to three radionuclide calibrators used for ^{68}Ga PET applications in a hospital are also shown.

Keywords: ^{68}Ga ; ^{22}Na ; nuclear medicine; calibration; TDCR method; activity measurement; radionuclide calibrator; PET.

1. Introduction

The radionuclide ^{68}Ga with a half-life equal to $67.83(20) \text{ min}^1$ is obtained using a $^{68}\text{Ge}/^{68}\text{Ga}$ generator, the ^{68}Ge half-life is $270.95(26) \text{ d}$. Gallium-68 labeled peptides have been recognized as a new class of radiopharmaceuticals showing fast target localization and blood clearance (Banerjee and Pomper, 2013). Particularly, they are currently in use for imaging and differentiating lesions of various somatostatin receptor subtypes, which are overexpressed in many neuroendocrine tumors.

Positron Emission Tomography (PET) has been just introduced in Cuba and its safety and effective application requires that all radioactivity measurements of the imaging procedure have to be traceable to national or international standards (Zimmerman, 2013). This paper describes the realization and dissemination of the ^{68}Ga activity measurement unit in the country.

2. Implementation of the Triple to Double Coincidence Ratio (TDCR) Method.

The TDCR liquid scintillation counting method (Broda et al., 1988) was used for the realization of the ^{68}Ga activity measurement. The ^{68}Ga was eluted from an Eckert & ZieglerTM $^{68}\text{Ge}/^{68}\text{Ga}$ generator with 0.1M HCl . With the aim of creating $[\text{GaCl}_4]^-$ and $[\text{GaCl}_6]^{3-}$, 4M HCl was added

¹ Hereafter, the values of the uncertainty of nuclear data are provided in parentheses, for a coverage factor $k=1$, and they referred to the corresponding last digits, i.e.: $67.83(20)$ means 67.83 with a standard uncertainty equal to 0.20 .

² Mention of commercial products in this paper does not imply recommendation or endorsement by the authors or their institution and is included for experimental information only.

to the elution, which was then absorbed onto AG1-X8 (200-400 mesh) Bio rad ion exchange resin (quaternary ammonium). Finally, the gallium-68 was eluted with Milli-Q water and the resulting purified solution, with a ^{68}Ga activity concentration approximately equal to $1.85 \text{ MBq}\cdot\text{mL}^{-1}$, was employed as the radioactive solution for calibration. The $^{68}\text{Ge}/^{68}\text{Ga}$ activity ratio of this solution, assessed by liquid scintillation counting (LSC), was equal to 2.56×10^{-4} with a standard uncertainty of 0.04×10^{-4} at the reference time selected in the middle of the 1.2 h time interval during which the standardization measurements were performed. Accordingly, the ^{68}Ge contribution had a negligible influence in the standardization process. Gamma spectrometry measurements were also performed and no radioactive impurities were detected.

A set of five calibration sources were prepared by the pycnometer technique adding masses of the ^{68}Ga solution between 40 and 50 mg into 20mL low-potassium glass vials containing 15 mL of Ultima GoldTM scintillation cocktail. The gravimetric measurements were performed with a SartoriusTM MC 210S balance whose calibration is traceable to the respective Cuban National Reference Standard.

Measurements were carried out with a commercial HidexTM counter using live counting times of 60 s per vial. Five cycles of measurements were made during a time interval of approximately 1.2 h. Typical count rates of the logical sum of double coincidences signals, after corrections for dead-time effects, varied between 20800 and 7800 s^{-1} .

In this work, all relevant ^{68}Ga nuclear data are taken from . The ^{68}Ga counting efficiencies of the logical sum of double coincidences were estimated with a developed FORTRAN code that considers for calculations the ^{68}Ga simplified decay scheme presented in Fig. 1A, as in Roteta, et al. (2012). The code uses the KLM atomic rearrangements model, the Poisson statistics for the photoelectron emissions and it takes into account the photomultipliers' asymmetry for calculations. The code also includes the Birks equation for ionization quenching as well as the Bethe formula for the stopping power at beta particle energies, E , higher than 100 eV. For

beta energies less than 100 eV, a direct proportionality of the stopping power to the energy E is assumed.

Counting efficiencies of the logical sum of double coincidences for β^+ and electron capture branches were dissimilar; the first being equal to unity while the latter approached a value of 0.75 for the experimental measurement conditions. In Fig. 2, the obtained dependence between the TDCR parameter and the overall counting efficiencies, ε_D , obtained by combining both contributions, is shown for the Birks' parameter, kB , equal to $0.011 \text{ cm}\cdot\text{MeV}^{-1}$. For ^{68}Ga measurements, the typical TDCR parameter was 0.963 and the typical calculated value of ε_D was 0.973 with a standard uncertainty equal to 0.008. A maximum variation of 0.001 is observed in this overall counting efficiency, when kB varies from 0.007 to $0.013 \text{ cm}\cdot\text{MeV}^{-1}$.

The estimate of the ^{68}Ga activity concentration at the reference time was $352.2 \text{ kBq}\cdot\text{g}^{-1}$ and its associated combined standard uncertainty was $3.5 \text{ kBq}\cdot\text{g}^{-1}$. This was derived from the mean of 5 results. The main components of the uncertainty budget corresponding to this estimate are presented in Table 1.

With the aim to validate the ^{68}Ga efficiency calculations, the TDCR method was also applied to an AmershanTM standard solution of ^{22}Na - a positron emitter with a half-life equal to $2.6029(8)$ a and a decay scheme similar to that of ^{68}Ga , shown in Fig. 1A, from the point of view of type of emitted particles detected in the measurement system (see Figs. 1A and 1B). In the issued certificate, the ^{22}Na activity concentration of the solution is declared as NIST-traceable and the reported value is equal to 504 kBq g^{-1} with an expanded uncertainty ($k=2$) of 0.82 % at the reference date January 1st, 2004 12:00 UTC. The ^{22}Na measurement samples were prepared in a similar way to that described for the ^{68}Ga standardization. The typical measured TDCR parameter for ^{22}Na was 0.995 and the typical calculated value of ε_D was 0.908 with a standard uncertainty equal to 0.005. As a result, a ^{22}Na activity concentration equal to 504.8 kBq g^{-1} was estimated by the TDCR method for the same reference date; the difference between this

measured value and the certified ^{22}Na activity concentration was equal to 0.16 %. The main components of the uncertainty budget corresponding to the ^{22}Na activity concentration estimate are also presented in Table 1.

3. The secondary standard radionuclide calibrator for ^{68}Ga measurements

A CapintecTM CRC-15R radionuclide calibrator is employed as a secondary standard. The results of the standardization of the ^{68}Ga solution by the TDCR method were used to derive the correction factors for ^{68}Ga activities measured in several geometries of interest in nuclear medicine; these correction factors are applied to the activity indicated by the instrument when the calibration setting provided for the secondary standard calibrator by the manufacturer is employed for measurements (Table 2). As can be seen, the relative combined standard uncertainty ($k=1$) estimates of the new calibration settings, considered as the combination of the manufacturer's calibration setting and the determined correction factors to be applied to the ^{68}Ga activity displayed by the instrument, were equal to 1.6 % (see Table 2). The uncertainty budget for these new calibration settings is presented in Table 3. Magnitudes of contributions due to measurement repeatability and the measurement time, which were significant for the estimated measurement uncertainty of new calibration settings, could be reduced if another experiment was performed. Indeed, measurement repeatability equal to 0.05 %, similar to the one reported for the parameter in Table 4 employing calibration sources with a ^{68}Ga activity in the order of 15- 20 MBq instead of the 1.4 MBq sources used this time, could probably be obtained due to the improvement of the counting statistics. In addition, an accuracy of the time measurements of ± 15 s can possibly be attained during the subsequent calibration, instead of the ± 1 min accuracy obtained for data reported in this paper. Using a rectangular distribution and the ± 15 s time accuracy value, a contribution of the uncertainty component due to measurement time equal to 0.15 % is used to obtain the overall uncertainty of the new calibration settings. Then, it is estimated that a relative combined standard uncertainty ($k=1$) of

^{68}Ga calibration settings could be equal to 1.4 % for the secondary standard radionuclide calibrator, taking into account the above-mentioned two improvements during the calibration procedure.

The main components of the combined uncertainty, $u_c(A_{I0})$, associated with the ^{68}Ga activity, A_{I0} , measured in the secondary standard calibrator are presented in Table 4. On the basis of these data, the activity of ^{68}Ga is measured with a combined standard uncertainty of 1.9 % at the secondary level. The uncertainty due to the calibration is the largest contribution to the uncertainty of the ^{68}Ga activity measurement and its value is typical for good quality ionization chambers (Schrader, 1997). Nevertheless, special attention needs to be paid to the uncertainty component of the time of measurement as variations of 1 or 2 minutes could result in a large uncertainty contribution to the measured ^{68}Ga activity, as explained above.

4. Transfer of the measurement unit to radionuclide calibrators for ^{68}Ga PET applications in a hospital

The transferring of the measurement unit to radionuclide calibrators utilized for ^{68}Ga PET applications in a Cuban hospital - the Institute of Oncology and Radiobiology - has been performed *in situ* in the hospital's facilities. The instruments are calibrated in the same locations and measurement conditions that are used in the clinical practice. For that purpose, the secondary standard radionuclide calibrator, previously calibrated for ^{68}Ga measurements, is used as a travelling standard and moved from CENTIS to the hospital facilities. Gallium-68 samples in geometries of interest are prepared *in situ* in the hospital from ^{68}Ga solutions obtained from Eckert & ZieglerTM $^{68}\text{Ge}/^{68}\text{Ga}$ generators available in the hospital for ^{68}Ga radiopharmaceutical preparations. Then, the ^{68}Ga activity in each sample is calibrated as a result of its measurement in the secondary standard radionuclide calibrator. Immediately after their calibration, ^{68}Ga samples are used to determine the calibration coefficients, f_{cal} , of the end-

users' radionuclide calibrators in geometries of interest for nuclear medicine applications (Table 5). The results presented in Table 5 summarize the outcomes of calibrations of radionuclide calibrators in use in the Institute of Oncology and Radiobiology performed during 2015 and 2016 by CENTIS personnel. As observed, when the manufacturer calibration settings are employed for measurements, the estimated correction factors for some measurement geometries of interest could be significant, especially in the context of the 10 % accuracy limit required in Cuba for this type of measurements (Guía, 2002). The uncertainty budget for f_{cal} , is also presented in Table 3. Using this uncertainty value for f_{cal} , it may be estimated that ^{68}Ga activities determined in the radionuclide calibrators of the end-users, when performed in accordance with adequate quality assurance measurement procedures, could be traceable to the liquid scintillation counting standard at the primary level of the national traceability chain with a combined standard uncertainty equal to 2.7 % (Table 4).

Conclusions

The realization of the ^{68}Ga activity measurement unit in Cuba was performed by the TDCR method using a commercial liquid scintillation counter HidexTM and a FORTRAN code developed for the calculation of the ^{68}Ga counting efficiencies in the given measurement system. The relative expanded uncertainty ($k=2$) associated to the ^{68}Ga activity concentration obtained with the method is equal to 2 %. With the aim to validate this measurement uncertainty estimate, the method was also applied to an Amersham standard solution of ^{22}Na - a positron emitter with a decay scheme similar to that of ^{68}Ga from the point of view of type of emitted particles detected in the measurement system. The ^{22}Na activity concentration, estimated by the TDCR method, had an expanded uncertainty ($k=2$) of 1.4 % and the corresponding reference value traceable to the NIST differed by 0.16 %.

The transfer of the ^{68}Ga activity unit realized with the TDCR method to the secondary standard radionuclide calibrator was performed with an expanded uncertainty ($k=2$) equal to 3.2 % for

measurement geometries of interest in nuclear medicine. The secondary standard radionuclide calibrator provides a travelling transfer standard that is moved from CENTIS to the hospital facilities for the calibration of end-users' instruments. Particularly, in 2015 and 2016, three radionuclide calibrators used for ^{68}Ga PET applications in a Cuban hospital were calibrated *in situ* in the hospital's facilities; the reference conditions were the same as the conditions employed during routine ^{68}Ga measurements in the clinical practice. The calibration outcomes of these three radionuclide calibrators indicate that when the manufacturer calibration settings are employed for measurements, the assayed ^{68}Ga activities in some measurement geometries of interest could not satisfy the 10 % accuracy limit required in Cuba for this type of measurement. It is estimated that the ^{68}Ga measurements determined in the radionuclide calibrators of end-users, when performed in accordance with adequate quality assurance measurement procedures, can be traced to the national reference within $\pm 5.4\%$ ($k=2$).

This work outcome provides the basis for compliance with the requirement that all radioactivity measurements of the imaging procedure need to be traceable to national or international standards as a premise for the safe and effective application of the ^{68}Ga radiopharmaceuticals in the country.

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Table 1. Uncertainty components in the standardization of ^{68}Ga and ^{22}Na by the TDCR method at CENTIS, expressed in % of the activity concentration, A .

Uncertainty component	Contribution in % of the A for ^{68}Ga	Contribution in % of the A for ^{22}Na
Counting statistics	0.14	0.12
Weighing	0.15	0.15
Dead time	0.10	0.10
Background	0.006	0.006
Pile-up	0.10	0.10
Counting time	0.30	negligible
Input parameters and statistical model	0.85	0.6
Quenching	0.20	0.20
Impurities	0.06	0.06
Radioactive decay	0.22	0.09
Source stability	0.20	0.1
Combined standard uncertainty ($k=1$)	1.0	0.7

Table 2. Results of the calibration of the secondary standard radionuclide calibrator for ^{68}Ga measurements in several geometries of interest in nuclear medicine.

Measurement geometry	Manufacture calibration setting ^a	Estimated correction factor	Relative standard uncertainty ($k=1$) of the new calibration setting ^b , in %
2R vial (ISO, 2003) with 0.7 mL of ^{68}Ga solution ^c	416	0.929	1.6
2R vial (ISO, 2003) with 1.1 mL of ^{68}Ga solution ^c	416	0.942	1.6
15R vial (ISO, 2003) with 6 mL of ^{68}Ga solution ^c	416	0.957	1.6
Plastic syringe 2.5 mL capacity with 2 mL of ^{68}Ga solution ^d	416	0.911	1.6
Plastic syringe 5 mL capacity with 2 mL of ^{68}Ga solution ^d	416	0.908	1.6

a Manufacture calibration setting is provided for NIST ampoule with 5 mL of radioactive solution.

b In this case, the new calibration setting is the combination of the manufacturer's calibration setting and the determined correction factor to be applied to the ^{68}Ga activity displayed by the instrument.

c The vial is placed at the bottom of the sample holder provided by the instrument manufacturer.

d The syringe is placed in the "syringe measurement position" of the sample holder provided by the instrument manufacturer.

Table 3 Uncertainty budgets for the calibration settings, f_{cal} , determined for the secondary standard radionuclide calibrator and a radionuclide calibrator at the end-user level.

Component, x_i	Secondary standard radionuclide calibrator $u(x_i)$ in %	End-user radionuclide calibrator $u(x_i)$ in %
Calibration sources	1.2	1.9
Scale resolution	0.2	0.1
Repeatability	0.6	0.5
Measurement time	0.6	0.6
Others (radioactive background, radioactive decay, electrometer zero, radioactive impurities, step size of the calibration setting)	0.6	0.6
Combined standard uncertainty of the calibration setting, $u_c(f_{cal})$ ($k=1$)	1.6	2.1

Table 4 Uncertainty budgets for the ^{68}Ga activities, A_{I0} , determined by the secondary standard radionuclide calibrator and end-user radionuclide calibrators.

Component, x_i	Secondary standard radionuclide calibrator $u(x_i)$ in %	End-user radionuclide calibrator $u(x_i)$ in %
Calibration coefficient	1.60	2.1
Long-term stability	0.22	1.0
Repeatability	0.05	0.5
Linearity	0.50	1.0
Scale resolution	0.06	0.1
Time of measurement	0.60	0.6
Radioactive background	0.05	0.1
Half-life	0.12	--
Other(radionuclide impurity content, sample stability and reproducibility of the measurement geometry)	0.60	0.6
Combined standard uncertainty of radionuclide activity, $u_c(A_{I0})$ ($k=1$)	1.9	2.7

Table 5 Outcome of calibrations of the end-user radionuclide calibrators for ^{68}Ga measurements in several geometries of interest in nuclear medicine.

Instrument model	Measurement geometry ^(a)	Manufacturer calibration setting	Estimated correction factor	New calibration setting, f_{cal}
PTW -Freiburg Curiementor 3	15R vial with 6 mL of ^{68}Ga solution	0.41	1.114	0.459
PTW -Freiburg Curiementor 3	Plastic syringe 2.5 mL capacity with 2 mL of ^{68}Ga solution	0.41 x 1	1.069	0.459 x 0.952
PTW -Freiburg Curiementor 3	Plastic syringe 5 mL capacity with 2 mL of ^{68}Ga solution	0.41 x 1	1.062	0.459 x 0.952
Capintec CRC 25 PET	15R vial with 6 mL of ^{68}Ga solution ^(c)	416	0.973	430
Capintec CRC 25 PET	Plastic syringe 2.5 mL capacity with 2 mL of ^{68}Ga solution ^(b)	416	0.923	463
Capintec CRC 25 PET	Plastic syringe 5 mL capacity with 2 mL of ^{68}Ga solution ^(b)	416	0.921	463
Capintec CRC 25 PET	Plastic syringe 5 mL capacity with 2 mL of ^{68}Ga solution into the syringe stainless steel shield ^(b)	416	3.882	43
Capintec CRC 25 PET	15R vial with 6 mL of ^{68}Ga solution	416	0.934	450
Capintec CRC 25 PET	Plastic syringe 2.5 mL capacity with 2 mL of ^{68}Ga solution	416	0.886	481
Capintec CRC 25 PET	Plastic syringe 5 mL capacity with 2 mL of ^{68}Ga solution	416	0.884	481
Capintec CRC 15R	15R vial with 6 mL of ^{68}Ga solution ^(b)	416	0.954	440
Capintec CRC 15R	Plastic syringe 2.5 mL capacity with 2 mL of ^{68}Ga solution ^(b)	416	0.919	463

Capintec CRC 15R	Plastic syringe 5 mL capacity with 2 mL of ^{68}Ga solution ^(b)	416	0.912	463
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(a) The ^{68}Ga calibrated sample is placed in the corresponding position in the sample holder provided by the manufacturer.

(b) The ionization chamber is inside a well designed for that purpose in a hot cell TEMA SINERGE™ for radiopharmaceutical preparation.

Figures Captions

Fig.1A The ^{68}Ga simplified decay scheme employed for counting efficiencies calculations with the developed FORTRAN code.

Fig. 1B The ^{22}Na decay scheme employed for counting efficiencies calculations with the developed FORTRAN code.

Fig. 2 Calculated dependence between the TDCR parameter and the overall counting efficiencies, ε_D , of ^{68}Ga , for the Birks' parameter k_B equal to $0.011 \text{ cm}\cdot\text{MeV}^{-1}$.

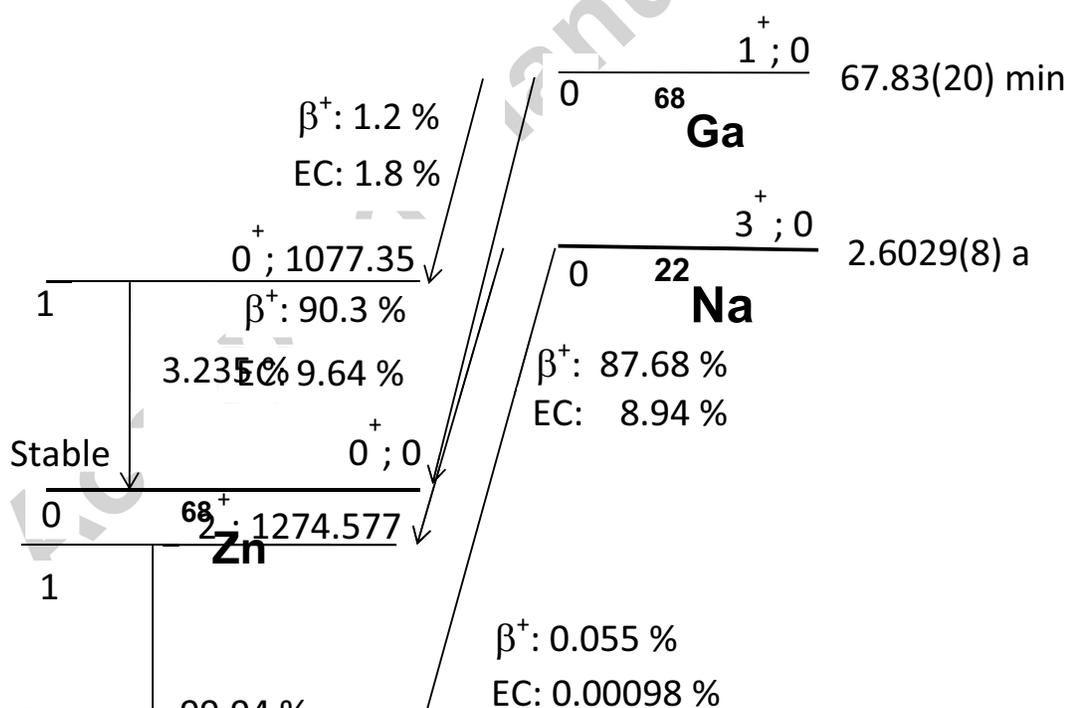
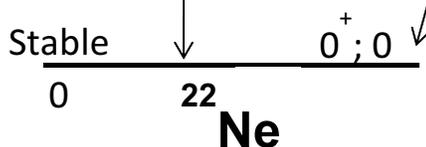
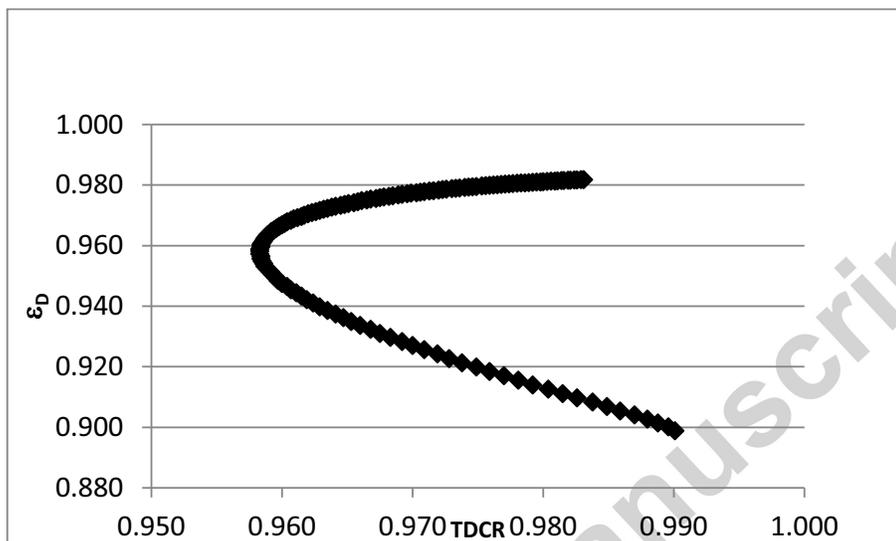
Fig. 1A**Fig. 1B**

Fig. 2



Highlights

- The TDCR method is described for ^{68}Ga using a HidexTM commercial LS counter.
- ^{68}Ga standard by TDCR transferred to Capintec CRCTM 15R radionuclide calibrator.
- ^{68}Ga standard transferred to 3 hospital radionuclide calibrators used for ^{68}Ga PET.