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Traceability from governmental producers of radiopharmaceuticals in measuring ^{18}F in Brazil

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HIGHLIGHTS

- Traceability to the Brazilian metrological chain in nuclear medicine.
- Application of the criteria from ISO/IEC17043:2011.

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ABSTRACT

Since the inception of its proficiency test program to evaluate radionuclide measurement in hospitals and clinics, the National Metrology Laboratory of Ionizing Radiation-LNMRI, that represents Brazilian National Metrology Institute (NMI) for ionizing radiation has expanded its measurement and calibration capability.

Requirements from the National Health Surveillance Agency from Ministry of Health (ANVISA), to producers of radiopharmaceuticals provided an opportunity to improve the full traceability chain to the highest level.

Fluorodeoxyglucose (FDG-^{18}F) is the only radiopharmaceutical simultaneously produced by all Brazilian radiopharmaceutical production centers (RPCs). By running this proficiency test, LNMRI began to provide them with the required traceability.

For evaluation, the ratio of RPC to reference value results and ISO/IEC17043:2010 criteria were used.

The reference value established as calibration factor on the secondary standard ionization chamber was obtained from three absolute measurements systems, and routinely confirmed in each round of proficiency test by CIEMAT/NIST liquid scintillation counting. The γ-emitting impurities were checked using a High-Purity Germanium (HPGe) detector.

The results show that Brazilian RPCs are in accordance with (accuracy within ± 10%) the Brazilian standard for evaluation of measurements with radionuclide calibrators (CNEN NN 3.05., 2013). Nevertheless, the RPCs should improve the methodology of uncertainty estimates, essential when using the statistical criteria of ISO/IEC 17043 standard, in addition to improving accuracy to levels consistent with their position in the national traceability chain

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1. Introduction

In Brazil, the government has a monopoly on mining of radioactive elements, production and trade in nuclear materials. This monopoly is operated and supervised by the National Nuclear Energy Commission (CNEN). One of CNEN's research units is the Institute for Radiation Protection and Dosimetry (IRD), which includes the LNMRI. This laboratory is, by law and by competence, which is demonstrated through the traceability measurements checked by the Bureau International des Poids et Measures (BIPM), the accredited institution of the National Institute of Metrology, Normalization and Industrial Quality (INMETRO-the Brazilian Legal and Scientific Metrology Organization) for the maintenance of standards and radioactivity measurements in Brazil.

Within LNMRI is the Radionuclide Metrology Laboratory (RML) whose main concerns are to:

I. Prepare and disseminate radioactive standards.
II. Improve accuracy of radioactivity measurements in the country.
III. Participate in international comparisons of radionuclide measurements.

Through the RML, LNMRI has been promoting a proficiency test program since 1997 (Iwahara et al., 2001) in order to evaluate radionuclide measurement performance in hospitals and clinics (NMSs – Nuclear Medicine Services). Such programs exist in several other countries, as described in Santry (1998) and Oliveira (2013).

Since the beginning of its program, the Brazilian NMI expanded its action creating regional laboratories to serve the large geometric area of Brazil, and presented several studies and reported progress in this area (Silva et al., 2014; Rezende et al. 2012; Tauhata et al., 2008; Dos Santos et al., 2004). These regional laboratories possess radionuclide calibrators whose calibration factors are traceable to the LNMRI and carry out comparison exercises with the NMSs located in its region. Fig. 1 shows the National Metrology Network of Radionuclides for comparisons of activity measurements in NMSs in Brazil. The numbers within brackets represents the number of NMSs in each major region

2. Brazilian interlaboratory comparison program

Radionuclide measurements carried out in Brazilian hospitals for medical applications of diagnosis and therapy must be traceable to the standards and measurements systems set up at LNMRI. This is a quality assurance program for the performance of measurements made in the hospitals with radionuclide calibrators (sometimes called dose calibrators of radionuclides or activity meters). Their performance is evaluated in the proficiency test runs by means of statistical comparative measures between hospitals and LNMRI and in accordance with regulatory requirements (Norms). Performance of radionuclide calibrators for ^{67}Ga, ^{99m}Tc, ^{123}I, ^{131}I, and ^{201}Tl were evaluated. These radionuclides have been standardized by absolute methods and the results adopted as the references for the proficiency tests and also to establish the national reference system based on a $4\pi\gamma$ ionization chamber.

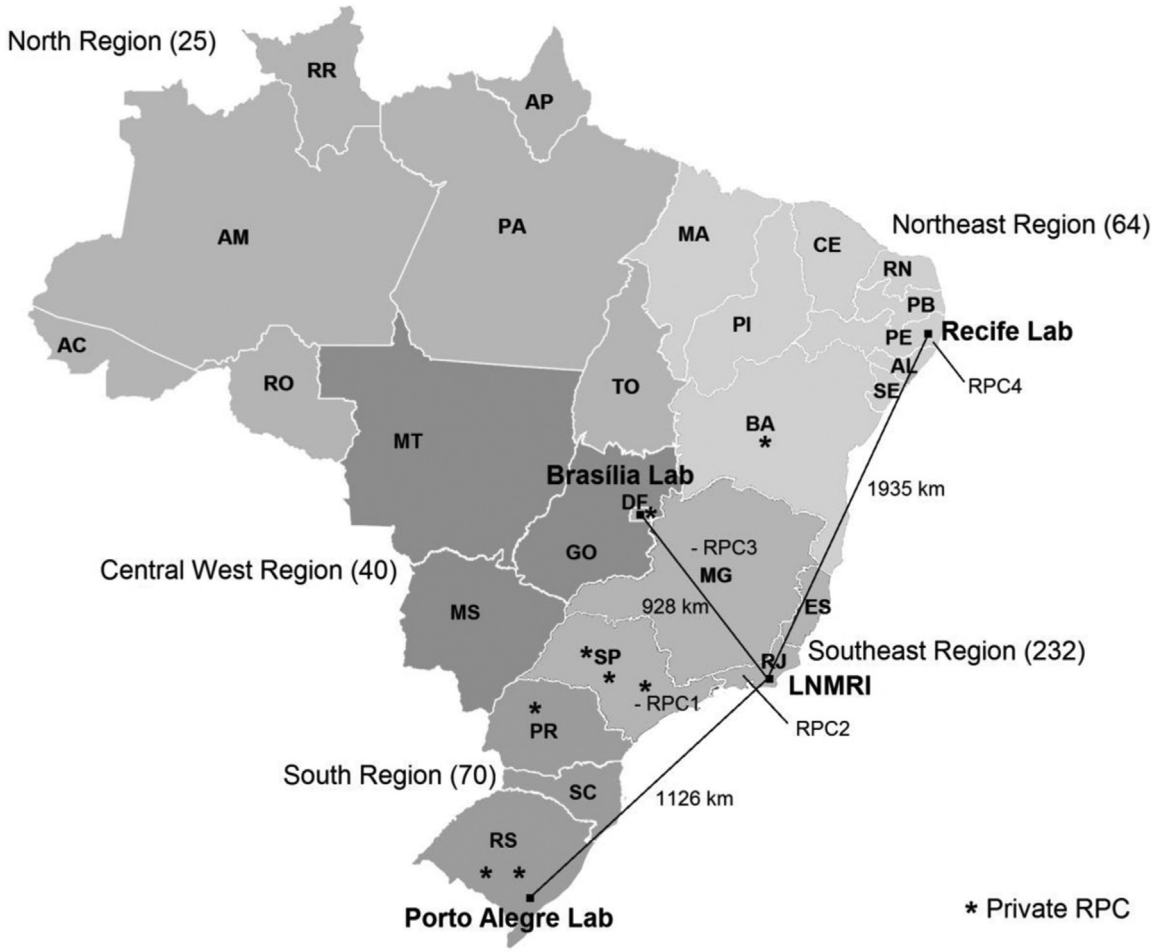

Fig. 1. National Metrology Network of Radioactivity measurements in Brazil. Numbers in parentheses indicate the number of NMSs in that region. Governmental RPCs (1–4).

Table 1
Statistical criteria adopted for performance evaluation according with ISO/IEC 17043 standard, and **R** value acceptance criterion of the Brazilian regulatory authority (CNEN, 2013).

Criterion	Calculated value	Compliance criterion
Accuracy (U_{score})	$U_{score}=\left\lvert \frac{value_{RPC}-value_{LNMRI}}{1.96\times\sqrt{u_{RPC}^2+u_{LNMRI}^2}} \right\rvert$	$\lvert \mathbf{U_{score}} \rvert \leq 1$
Precision (P)	$P=\sqrt{\left(\frac{u_{RPC}}{value_{RPC}}\right)^2+\left(\frac{u_{LNMRI}}{value_{LNMRI}}\right)^2}\times 100\%$	$\mathbf{P} \leq 5\%$
Percentage Difference ($D_{\%}$)	$D_{\%}=\frac{value_{RPC}-value_{LNMRI}}{value_{LNMRI}}\times 100\%$	$\mathbf{D_{\%}} \leq \pm 10\%$
Z_{score}	$Z_{score}=\frac{value_{RPC}-value_{LNMRI}}{\sigma}$ $\sigma = 0.05 \times value_{LNMRI}$	$\lvert \mathbf{Z_{score}} \rvert \leq 2$
R	$R=\frac{value_{RPC}}{value_{LNMRI}}$	$0.9 \leq \mathbf{R} \leq 1.1$

Located in the state of Rio de Janeiro, LNMRI is able to provide direct assistance only to the NMSs in this state (46). In the same Southeast region, Espirito Santo state (14), Minas Gerais state (56) and São Paulo state (116) do not have regional labs to serve them. As an alternative method, a round of proficiency tests was held with the Brazilian NMS for ^{123}I, ^{131}I and ^{99m}Tc, with sources sent by two RPCs in the southeast area (Iwahara et al., 2002). This method will continue to be tested as the next step of this work, because it has great potential to avoid the logistic problems involved in managing the proficiency test program in a large country.

These comparison exercises also establish traceability of activity measurements for nuclear medicine practices in the country and may be used to take corrective and preventive actions to improve the quality of services afforded to the patients.

3. Intercomparison program with ^{18}FDG producers

The entire traceability chain needed from the production of the radiopharmaceutical until administration to the patient in Brazil is regulated by ANVISA. The board of ANVISA has approved resolutions establishing the minimum requirements to be observed in the manufacture of radiopharmaceuticals, which must comply with the Good Manufacturing Practices and also with the basic principles of Good Manufacturing Practices (GMP) of Medicines. These GMPs are documented in ANVISA (2009) and ANVISA (2010).

LNMRI manages this program of comparisons with government center producers to demonstrate the traceability of their activity measurements of radiopharmaceuticals containing ^{18}F, ^{67}Ga, ^{99m}Tc, ^{123}I, ^{131}I, and ^{201}Tl using radionuclide calibrators. Verification of the half-life and impurities are also essential in order to avoid misunderstandings or differences which result in an unnecessary increase in dose to the patient.

Due to the half-life and application in cardiology and neurology, ^{18}F is widely used in the synthesis of radiopharmaceuticals. Being a positron emitter, it allows refined techniques of obtaining tomographic images. As ^{18}F is the only radiopharmaceutical produced by all Brazilian RPCs, from the start an intercomparison program with this radionuclide will involve all producers in the country. This program will be extended in the future to other private producers that started to produce ^{18}F following the break-up of the monopoly for radionuclides with short half-life such as ^{18}F and others.

The results of the intercomparison programs can be evaluated by two methods:

a) By using the value of the ratio R which is the value obtained from the RPC activity value, divided by the activity value obtained by LNMRI. The acceptance criterion of the Brazilian regulatory authority for a NMS is that $0.9 \leq \mathbf{R} \leq 1.1$ (CNEN, 2013).
b) By using ISO/IEC17043 proficiency test criteria (ABNT NBR ISO/IEC 17043, 2011) that is defined below.

Proficiency testing is defined in ISO/IEC 17043 as the evaluation of participant performance in interlaboratory comparisons by means of pre-established criteria.

When performed in the context of a comprehensive quality assurance program, proficiency testing is an independent means to assure the quality of the test and calibration results, as recommended in ISO/IEC 17025.

In order for all the results from RPC to be designated as “Acceptable”, all of the individual criteria have to be “Acceptable” as well. The final result of the performance evaluation is defined by the combined results of ISO/IEC 17043 criteria (*Accuracy, Precision, percentage difference* and Z_{Score}). Table 1 shows the mathematical formulations of these criteria as described in Iwahara et al. (2009).

For all calculations, $value_{LNMRI}$ is the LNMRI reference value, established for each test run; $value_{RPC}$, is the mean value of five RPC activity measurements for each sample; u_{LNMRI}, is the combined standard uncertainty ($k=1$) of the reference value; u_{RPC}, is the total standard uncertainty ($k=1$) of RPC measurements. In the accuracy formula the 1.96 value is the coverage factor for a confidence level of 95%. In the Z_{score} formula, σ is the expected standard deviation for proficiency assessment, which is conservatively computed as 5% of $value_{LNMRI.}$

In order to fulfill its mission as the Brazilian NMI, LNMRI has standardised the radionuclide ^{18}F using three absolute methods: 4πβ(LS)-γ(NaI (Tl)) coincidence and anti-coincidence methods and peak sum method (Oliveira, 2012; Silva et al., 2014). After five rounds of comparisons with converging results the anti-coincidence method result was retained in the CENTRONIC IG11 ionization chamber for the routine measurements, due its consistent repeatability. The conservative combined uncertainty for the anti-coincidence method result was 0.58% of activity per mass, and for the calibration factor of the IG11 the combined uncertainty was 0.65%.

The LNMRI reference system CENTRONIC IG11 is a well-type ionization chamber with a filling gas of argon at a pressure of 2 MPa and it is coupled to a 6517 A Keithley electrometer which is controlled by a homemade LabVIEW program. For activity determination using this equipment, two samples are prepared by dispensing around 2.6 g into a flame sealed LNMRI ampoule. Radiopharmaceuticals are measured in glass vials at the RPC and then are sent to the NMS. These vials, which have a larger diameter and thickness than the LNMRI ampoule, are measured in a CENTRONIC IG12 ionization chamber, which has been cross-calibrated to the CENTRONIC IG11. These results obtained in the LNMRI chambers will be compared with those from the RPC.

For each intercomparison round, the RPC prepares two glass vials containing the FDG solution, measures them in their own radionuclide calibrator and then sends them and their measured activity values to the LNMRI. The glass vials are measured in the CENTRONIC IG12 ionization chamber. One of the glass vial received from the RPC is opened and its content used to prepare samples to be measured. Two LNMRI ampoules are prepared with approximate masses of 0.5 and 1.0 g of active solutions and then topped up with inactive carrier to the required height. The ampoules are measured for activity determination in the CENTRONIC IG11 ionization chamber and for impurity determination in a planar germanium detector Canberra, model GL2020 R. One source, with approximately 3 g, is also prepared in an internationally used Schott 10 R glass vial (standard geometry of LNMRI), and topped

Table 2
Evaluation of results for RPC1 Glass vial GI-PHARMA.

Source	Radionuclide calibrator model	Value (MBq)	Uncertainty (%) ($k=1$)	Ratio R	U_{score}	Precision (%)	Percentage difference $D_{\%}$	Z_{score}
				[0.9; 1.1]	**$\|U\| \leq 1$**	**$P \leq 5\%$**	**[−10; +10]**	**$\|Z\| \leq 2$**
S1	IG11 CRC-15R	107.78 107.99	0.29 2.06	1.00	0.05	2.1	0.20	0.04
S1	IG12 CRC-15R	108.84 107.99	0.48 2.06	0.99	0.19	2.1	−0.78	0.16
S2	IG12 CRC-15R	104.33 102.04	0.47 2.05	0.98	0.54	2.1	−2.19	0.44

Table 3
Evaluation of results for RPC1 Glass vial Own.

Source	Radionuclide calibrator model	Value (MBq)	Uncertainty (%) ($k=1$)	Ratio R	U_{score}	Precision (%)	Percentage difference $D_{\%}$	Z_{score}
				[0.9; 1.1]	**$\|U\| \leq 1$**	**$P \leq 5\%$**	**[−10; +10]**	**$\|Z\| \leq 2$**
S1	IG11 CRC-15R	102.83 101.43	0.30 2.06	0.99	0.34	2.1	−1.36	0.27
S1	IG12 CRC-15R	102.27 101.43	0.48 2.06	0.99	0.20	2.1	−0.83	0.17
S2	IG12 CRC-15R	110.36 110.15	0.47 2.04	1.00	0.05	2.1	−0.19	0.04

Table 4
Evaluation of results for RPC2 Glass vial Own.

Source	Radionuclide calibrator model	Value (MBq)	Uncertainty (%) ($k=1$)	Ratio R	U_{score}	Precision (%)	Percentage difference $D_{\%}$	Z_{score}
				[0.9; 1.1]	**$\|U\| \leq 1$**	**$P \leq 5\%$**	**[−10; +10]**	**$\|Z\| \leq 2$**
S1	IG11 CRC-15-ULTRA	121.32 119.91	0.32 1.24	0.99	0.47	1.3	−1.16	0.23
S1	IG12 CRC-15-ULTRA	121.87 119.91	0.47 1.24	0.98	0.63	1.3	−1.61	0.32
S2	IG12 CRC-15-ULTRA	119.78 121.85	0.47 1.24	1.02	0.66	1.3	1.73	0.35

up to 4 g with inactive carrier. This source is measured in the CENTRONIC IG12 ionization chamber. Finally, 8 sources are prepared of about 10 mg each added to 10 ml of scintillation solution to check the activity in a liquid scintillation counter.

4. Results

Results of checked activity in the liquid scintillation counter did not show significant differences in comparison with those determined by the IG11 ionization chamber.

The results of the comparison tests with each RPC are presented in Tables 2–7.

S1 in the Source column refers to the sample opened to prepare different geometries of measurement. S2 refers to the unopened sample. IG11 in the column of radionuclide calibrator model refers to results of the CENTRONIC IG11 measured in LNMRI ampoules. IG12 at the same column refers to results of the CENTRONIC IG12 measured directly at glass vials as sent by RPCs. The RPC1 uses calibrator CAPINTEC CRC-15R and RPC2 uses calibrator CAPINTEC CRC-15R ULTRA. Two other producers that use an automatic system for the distribution of radiopharmaceuticals in syringes and vials, named THEODORICO from COMECER SPA Company, did not have identification of the radionuclide calibrator. The manuals describe necessary information like the physical characteristics of the chamber, range and response of the electrometer and performance of the whole system.

All the **R** results meet acceptance criterion of the only available Brazilian standard to assess the performance of radionuclide calibrator of $0.9 \leq \mathbf{R} \leq 1.1$. This legal acceptance criterion seems not be enough because it is directed to NMSs. The RPCs are at a higher level of the metrological chain than the NMSs, and should

Table 5
Evaluation of results for RPC2 Glass vial GI-PHARMA.

Source	Radionuclide calibrator model	Value (MBq)	Uncertainty (%) ($k=1$)	Ratio R	U_{score}	Precision (%)	Percentage difference $D_{\%}$	Z_{score}
				[0.9; 1.1]	**$\|U\| \leq 1$**	**$P \leq 5\%$**	**[−10; +10]**	**$\|Z\| \leq 2$**
S1	IG11 CRC-15-ULTRA	69.57 67.81	0.33 1.32	0.97	0.97	1.4	−2.52	0.50
S1	IG12 CRC-15-ULTRA	69.44 67.81	0.50 1.32	0.98	0.87	1.4	−2.35	0.47
S2	IG12 CRC-15-ULTRA	69.37 67.80	0.46 1.25	0.98	0.88	1.3	−2.26	0.45

therefore have better traceability to the NMI than those. All results

Table 6
Evaluation of results for RPC3 Glass vial GI-PHARMA.

Source	Radionuclide calibrator model	Value (MBq)	Uncertainty (%) ($k=1$)	Ratio R	U_{score}	Precision (%)	Percentage difference $D_{\%}$	Z_{score}
				[0.9; 1.1]	**$\|U\| \leq 1$**	**$P \leq 5\%$**	**[−10; +10]**	**$\|Z\| \leq 2$**
S1	IG11 THEODORICO	88.60 96.49	0.32 2.32	1.09	**1.78**	2.3	8.91	1.78
S1	IG12 THEODORICO	87.93 96.49	0.50 2.32	1.10	**1.91**	2.4	9.74	1.95
S2	IG12 THEODORICO	111.10 103.67	0.46 2.33	0.93	**1.54**	2.4	−6.68	1.34

Table 7
Evaluation of results for RPC4 Glass vial GI-PHARMA.

Source	Radionuclide calibrator model	Value (MBq)	Uncertainty (%) ($k=1$)	Ratio R	U_{score}	Precision (%)	Percentage difference $D_{\%}$	Z_{score}
				[0.9; 1.1]	**$\|U\| \leq 1$**	**$P \leq 5\%$**	**[−10; +10]**	**$\|Z\| \leq 2$**
S1	IG11 THEODORICO	400.53 384.46	0.30 2.83	0.96	0.75	2.8	−4.01	0.80
S1	IG12 THEODORICO	400.10 384.46	0.51 2.83	0.96	0.72	2.9	−3.91	0.78
S2	IG12 THEODORICO	405.72 394.66	0.51 2.83	0.97	0.50	2.9	−2.73	0.55

for Accuracy (U_{score}) of the RPC3 (Table 6) are out of the compliance criterion shown in Table 1, even after recalculation of the uncertainties (see below). The results for Accuracy (U_{score}) of the RPC4 (Table 7) that were also out of the compliance criteria became acceptable after recalculating uncertainties correctly. The consistency of the RPC3 and RPC4 results are being checked in order to diminish percentage deviations from reference values. This difference may be understood by the fact that the pipe feeding the vial was within of the radionuclide calibrator cavity, with radioactive solution during measurement. In order to have acceptable traceability mainly for RPC3 (but taking care of RPC4) all these measurements will be repeated, under improved conditions.

5. Discussion

The difficulties with the geographical dimensions of Brazil and the number of NMSs not serviced in the country, beyond the requirements of ANVISA for release of radiopharmaceuticals, create an opportunity to ensure that the LNMRI provide traceability to the entire metrological chain from the International System of units (SI) to the end users, through RPCs.

Calculations from results the first ^{18}F proficiency test, taking into account the criteria of ISO/IEC 17043, showed that RPC1 had two bad results for accuracy (U_{score}). As this criterion depends on the uncertainties associated with the measurements, which is fundamental to providing traceability, RPC1, RPC3 and RPC4 were encouraged to recalculate the uncertainties that seemed to be too low for a commercial calibrator (as Capintec CRC-15R) which in good conditions could be within 3%. That can be seen in RPC2 results. Detailed information received after that the recalculation of uncertainties, improved the results obtained for RPC1 and for RPC3 and RPC4 that use THEODORICO radionuclide calibrators. The recalculated results indicate that in front of U_{score} criterion RPC3 measurements are still not acceptable. The main reason is

that the difference between RPC3 activities value and the reference value are too high (around 10%).

6. Conclusion

As is already done in many countries, it is more appropriate to change the model of evaluating the quality of NMSs of Brazil, by the qualification of the RPCs so they can act with safety and be linked into the metrological chain. All RPCs must follow the basic requirements for their measurements, so that their results stay within 5% relative to LNMRI reference, as a quality requirement. They should also provide all the tests concerning the technical conditions of radionuclide calibrators to allow an accurate evaluation of their measurements.

The quality assurance program adopted must be faithfully followed to reach acceptable results for all technical requirements. The adoption of a traceability chain model, where the LNMRI evaluates the RPCs and these cooperate in the assessment of the NMSs, and the creation of regional laboratories to serve the other states of the country will allow closer attention to the needs of NMSs and subsequent improvement in their performance to the comparison with reference. The results of the comparisons with the RPCs are promising and must be improved with more intense work, organization and training on the steps which have failed; mainly experimental procedures and uncertainties calculations.

Based on the international literature (IAEA, 2006; Oropesa et al., 2008) and in Brazilian accumulated experience that gives an indication of potential needs or training requirements for technician personnel in the measurement control at RPCs and NMSs, this work indicates maximum deviations from reference values of 2% for Regional laboratories, 5% for RPCs and 10% for NMSs, (this last, due CNEN NN-3.05 Brazilian Norm) to be quickly approved. Then, CNEN and ANVISA must apply quality assurance programs to upgrade personnel performance and qualification.

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