Applied Radiation and Isotopes 134 (2018) 64–67

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Rapid and accurate assessment of the activity measurements in Brazilian hospitals and clinics

A.E. de Oliveira[a,*], A. Iwahara[a], P.A.L. da Cruz[a], C.J. da Silva[a], E.B. de Araújo[b], J. Mengatti[b], R.L. da Silva[a], O.L. Trindade[a]

[a] Laboratório Nacional de Metrologia das Radiações Ionizantes (LNMRI), Instituto de Radioproteção e Dosimetria (IRD), Comissão Nacional de Energia Nuclear (CNEN), Av. Salvador Allende, s/n - Barra da Tijuca, CEP - 22783-127 Rio de Janeiro, RJ, Brasil

[b] Centro de Radiofarmácia (CERAF), Instituto de Pesquisas Energéticas e Nucleares (IPEN), Comissão Nacional de Energia Nuclear (CNEN), Caixa Postal 11049, CEP 05422-970 São Paulo, Brazil

HIGHLIGHTS

- Traceability to the Brazilian metrological chain in nuclear medicine.
- Adequate tool for assessing the quality of I-131 measurements in Hospitals and Clinics.
- Showed that geographical obstacles can be overcome for short-lived radionuclides.
- Demonstrated improvement in performance by participation in proficiency tests.
- Indicated need for training and advice in the estimation of uncertainties.

ARTICLE INFO

Keywords:
Traceability
Intercomparisons
Quality control
Radionuclide calibrator
^{131}I
Activity
Nuclear medicine service

ABSTRACT

Traceability in Nuclear Medicine Service (NMS) measurements was checked by the Institute of Radioprotection and Dosimetry (IRD) through the Institute of Energy and Nuclear Research (IPEN). In 2016, IRD ran an intercomparison program and invited Brazilian NMS authorized to administer ^{131}I to patients. Sources of ^{131}I were distributed to 33 NMSs. Three other sources from the same solution were sent to IRD, after measurement at IPEN. These sources were calibrated in the IRD reference system. A correction factor of 1.013 was obtained. Ninety percent of the NMS comparisons results are within ±10% of the National Laboratory of Metrology of Ionizing Radiation (LNMRI) value, the Brazilian legal requirement.

1. Introduction

Nuclear medicine is critically dependent on the accurate, reproducible performance of radionuclide measurements in hospitals and clinics. This kind of measurements performed using a National Metrology Institute (NMI) as a reference can provide traceability to higher level of the measurement chain. A Quality Control of Radionuclide Calibrators Program, defined as an established set of ongoing measurements and analyses designed to ensure that the performance of a procedure or instrument is within a predefined acceptable range, must be set up in order to asses routine medical measurement practice. These requirements for the quality control of activity assays in nuclear medicine can be fulfilled by calibrations made by direct comparisons with standards and with proofs that results of these tests and checks of the Radionuclide Calibrators have good performance. Therefore it is strongly recommended to participate in comparisons of activity measurements organized by national authorities or organizations, for example by the NMI or a calibration service traceable to it (Schrader, 1997). One of the main difficulties to this recommendation in Brazil is the distribution of reference samples, taking into account the country surface of about 8.5 million square kilometers and with some cities distant more than 4000 km from others. To overcome such difficulty in 2002 the Brazilian quality control program promoters implanted the Regional Laboratories (REGLABs). Two of them, DF and PoA received a Radionuclide Calibrator model Capintec CRC-15R and the third one, PE received a Centronic IG12 ionization chamber; each chamber had traceability to ^{201}Tl, ^{131}I, ^{123}I, ^{99m}Tc and ^{67}Ga measurements provided by Radionuclide Metrology Laboratory from IRD. These three labs and the IRD, acting as a regional laboratory in Rio de Janeiro, constitute a network to start to attend Brazilian needs. Fig. 1 shows

* Corresponding author.
E-mail address: aedu@ird.gov.br (A.E. de Oliveira).

http://dx.doi.org/10.1016/j.apradiso.2017.07.065
Received 11 March 2017; Received in revised form 13 July 2017; Accepted 31 July 2017
Available online 01 August 2017

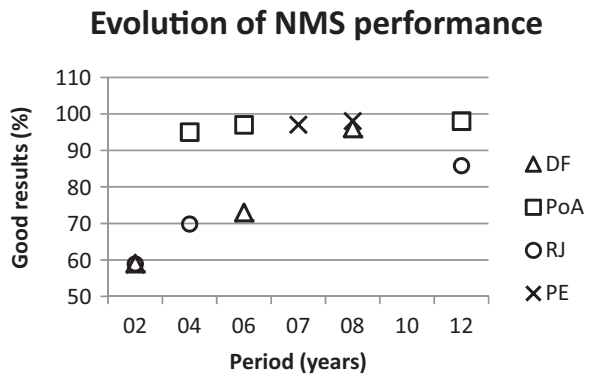

Fig. 1. Evolution of NMS performance.

performance of NMS evaluated by three REGLABs and by IRD. DF, PoA and PE are REGLABs in the center west, south and northeast, respectively while IRD is in the southeast (RJ). The y-axis (good results) represents the percentage of participants whose results were within 10% of the REGLAB value. According to these results, REGLABs have helped to improve performance of hospitals and clinics participants of the Quality Control Program, but their reach was limited to a few dozens of kilometers, because of the need to go by car. It means, in today's numbers, that REGLABs would attend to less than 25% hospitals and clinics of the country (De Oliveira et al., 2016).

Overcoming these limitations would require IRD to invest in infrastructure (staff, equipment, transports, etc.) but this option is not available at present due to technical and economic conditions. Another solution could be a calibration service traceable to IRD attending to the NMS in accordance with a National Standard. This second option isn't available in Brazil yet but IRD is currently applying resources, time, and effort to implement this solution.

At this work, the adopted strategy to support traceability needs for NMS to IRD is to implement a comparison having a radiopharmaceutical producer as a link between these two levels of the metrological chain. As this producer has national reach, routinely distributing radiopharmaceuticals for diagnosis and therapy, this methodology can give a rapid evaluation of the activity measurements in hospitals and clinics. With the guarantee of traceability of the producer's measurements to LNMRI, this assessment becomes accurate.

This methodology was developed to enable Brazilian NMS participation in the International Atomic Energy Agency program as part of the Latin American and Caribbean project, ARCAL RLA 6074 (ARCAL, 2016), which supports the development of regionally produced therapeutic radiopharmaceuticals for cancer therapy, organizes the comparison of the measurements of the activity of the therapeutic radionuclides using radionuclide calibrators. The project is based on the exchange of skills and knowledge, improvement of facilities, training and works on regional networks, so that the comparison exercise is organized under the premise of achieving shared use of metrological infrastructures, production and distribution of existing radiopharmaceutical products in Latin America and the Caribbean.

2. Materials and methods

2.1. Participants

Among the 429 NMSs in Brazil about 330 invitations were sent to those NMSs that are authorized to handle unsealed radioactive sources of ^{131}I for purposes of diagnosis or therapy in nuclear medicine. Ten percent of invited NMS accepted to participate in the intercomparison. As these NMSs were well distributed in the country, this percentage can be treated as the minimum to survey the state of art of NMSs measurements in the country. Some of these have proposed to submit measurements on more than one radionuclide calibrator used in the NMS. To all of them were given detailed instructions on the measurements to be performed and the results to be reported.

The following records were requested:

1. Name of NMS, name and e-mail of the contact person.
2. Brand, model and some specifications of the radionuclide calibrator (s).
3. Identification of the source received.
4. Date, time and results of 10 measurements of background radiation, ^{131}I source and control source (^{133}Ba or ^{137}Cs).
5. Calculation of the uncertainties of measurements according to the given guidelines sent by ARCAL program. (calibration factor, linearity, repeatability, background radiation, stability, other components and combined uncertainty)

The procedure used was to request IPEN, based in São Paulo, to prepare, measure and distribute sources of ^{131}I (half-life: 8.0233 d) to participant NMSs in all country and to IRD.

2.2. Source preparation

The items of the comparison were neutral glass bottles of 17 ml capacity, with dimensions 26.5 mm (diameter) × 1.10 mm (wall thickness) × 58.0 mm (main body height), type 1, as usually used by IPEN for the distribution of radiopharmaceuticals in Brazil. The vials contain 5 ml of a solution of the radionuclide of interest. For ^{131}I, a solution of Na^{131}I had a nominal activity of 185 MBq at the time of shipment to the participant.

After being prepared, the items were measured in the Capintec CRC-15R radionuclide calibrator of the IPEN, whose measurements are traceable to the IRD reference system (well-type Ionization Chamber).

All sources of this work, obtained from the same mother solution, were previously measured at IPEN at the same day (08/22/2016) between 14:49 and 15:59 h, after measurements they were sent to NMS and were received by them across the country until late afternoon the next day.

Additionally IPEN measure three radioactive sources of ^{131}I from the same solution in the Capintec CRC-15R radionuclide calibrator and sent them to IRD. One source was opened, prepared and calibrated in the IRD reference system (well-type Ionization Chamber Centronic IG11) and had its activity confirmed by measuring with the CIEMAT-NIST system. The opened sample was prepared as already described (De Oliveira et al., 2016). The two not opened samples were measured at well-type Ionization Chamber Centronic IG12, which has measurements traceable to IRD reference system. With this calibration, the correction factor for relating to the IRD's value was obtained. This factor was applied to measurements performed by IPEN to evaluate the performance of measurements of NMSs.

2.3. Calculation of data

The acceptance criterion of the Brazilian regulatory authority for a NMS is ($0.9 \leq R \leq 1.1$) (CNEN, 2013).

$$R = \frac{Activity\ at\ NMS^{*a}}{Activity\ at\ IPEN^{*b}} \quad (1)$$

where, ^{*a} – Corrected for the reference date. ^{*b} – Corrected for the reference date and LNMRI correction factor (FC).

$$FC = \left(\frac{activity\ at\ IPEN}{activity\ at\ IRD}\right)_{\text{Corrected for the reference date}} \quad (2)$$

The Z-Score shows how far a measurement value departs from the target value in terms of a target standard deviation. The formula for calculating the standard score is given by (ISO/IEC 17043, 2011):

$$Z_{score} = \frac{value_{NMS} - value_{IPEN}}{\sigma} \quad (3)$$

where $\sigma = 0.05 * value_{IPEN}$

In this case, the target value is the IPEN value and the target standard deviation is a value which can normally be expected to be achieved using a radionuclide calibrator. An acceptable Z-score is one that falls in the range of $|Z| \leq 2$. For $2 < |Z| < 3$ is questionable and not acceptable for $|Z| \geq 3$. For Brazilian NMSs, where the norm permits difference to reference value until 10% (CNEN, 2013), the used range of Z is $-3 < Z < +3$ and this corresponds to 99.72% of the area under the Normal Distribution curve. Due to the diverse purposes of proficiency test schemes it is not possible to define a single universal evaluation method. Therefore, a number of statistical designs used for the evaluation of performance are available (ISO/IEC 17043, 2011). The following approach for evaluation of performance was used: one questionable Z value ($2 < |Z| < 3$) can be acceptable and is considered as warning signal in a single proficiency test round. Questionable Z value in two successive rounds shall be taken as evidence that anomaly that requires investigation has occurred (Rosario et al., 2007).

3. Results

According to the number of radionuclide calibrators that were intended to participate in the comparison, 45 values of the R ratio would be possible. However, two NMSs did not send results, leaving 42 individual results from 30 NMSs.

The correction factor obtained according to Eq. (2) was 1.013, which means a difference of 1.3% between the IRD and IPEN results. This result was obtained with the sample opened. However, the results of the two other not opened samples had similar difference. The results are similar because the 3 samples are aliquots obtained from the same parent source. The measurement results of the two unopened samples on IC-IG12 are traceable to IC-IG11.

Table 1 presents the NMS results. All participants reported results in the mCi unit.

All of the results were corrected to the same reference time, taking into account the time zones and are presented in the MBq unit.

Participants reported the results of uncertainty incompletely and these calculations are being remade by exchanging information with them in order to calculate uncertainty independently.

Of the NMS results, 15 differ less than 2% from the reference value,

Table 1
Results of the bilateral IPEN-NMS comparison referenced by IRD. Reference date, t_{ref} (UTC) 2016/08/22 03:00 P.M.

Participant	Radionuclide calibrator	Reported Activity, $A_{measured}$ (mCi)	Reported u_{cr} ($A_{measured}$) k = 1 (%)	$Activity_{measured.}$ Corrected ($t_{ref.}$) [MBq]	Reference Activity, A_{ref} (t_{ref}) [MBq]	u_c (A_{ref}) k = 1 [MBq]	R Compliance criterion: $0.9 \leq R \leq 1.1$	Z_{score} Compliance criterion: $\|z\| < 3$
23	AN ACT 15P	5.2	0.1	213	225	0.9	0.948	− 1.58
24	C-CRC 7	4.7	0.6	220	221	0.9	0.995	− 0.16
25	V-VEXCALL-192	5.7	NR	232	223	0.9	1.043	1.32
26	C-CRC-15R	4.9	0.0	200	199	0.8	1.009	0.27
27	BMS - A100P	4.8	5.2	196	221	0.9	0.886	− 3.46
28	V-VEXCAL	4.5	2.7	220	204	0.8	1.079	2.38
29	C-CRC-35R	4.6	0.3	203	225	0.9	0.902	− 2.97
29*	C-CRC-25R PET	5.3	0.0	237	225	0.9	1.053	1.61
29**	C-CRC-25R	4.6	0.2	206	225	0.9	0.918	− 2.49
29***	C-CRC-25R	4.4	0.1	194	225	0.9	0.864	− 4.11
30	C-CRC-15R	4.4	NR	233	228	0.9	1.022	0.66
31	AN ACT 15P	4.3	0.0	225	219	0.9	1.026	0.79
32	FB MARK VI	5.5	9.0	225	225	0.9	0.997	− 0.08
33	V-AV-02	5.3	1.1	232	223	0.9	1.041	1.25
34	C-CRC-25R	5.6	7.0	228	223	0.9	1.021	0.64
35	BMS - A100P	5.1	0.1	209	226	0.9	0.928	− 2.20
36	V-AV-02	1.8	4.6	240	225	0.9	1.069	2.09
37	C-CRC-127 R	5.4	1.9	215	220	0.9	0.977	− 0.70
38	AN ACT-15P	1.7	0.1	226	221	0.9	1.018	0.55
39	AN ACT-15P	1.9	0.0	237	227	0.9	1.041	1.25
40	BMS - A100P	3.9	0.9	161	230	0.9	0.698	− 9.15
41	NA MARK V	5.2	0.0	230	229	0.9	1.006	0.18
41*	NA MARK V	2.3	NR	227	229	0.9	0.992	− 0.23
41**	C-CRC-25R	5.3	1.6	236	229	0.9	1.029	0.89
41***	C-CRC-25R	2.4	1.6	237	229	0.9	1.034	1.03
41****	C-CRC-25R PET	5.2	1.6	232	229	0.9	1.014	0.41
41*****	C-CRC-25R PET	2.4	1.6	234	229	0.9	1.022	0.66
41******	C-CRC-5	5.4	1.6	240	229	0.9	1.046	1.41
41*******	C-CRC-5	2.4	1.6	232	229	0.9	1.012	0.37
42	BMS - A100P	4.8	2.0	232	230	0.9	1.007	0.22
42*	C-CRC-25R PET	4.9	3.1	236	230	0.9	1.024	0.72
43	C-CRC-25R	6,0	1.0	237	232	0.9	1.025	0.76
44	V-VEXCAL	4.7	16.4	210	222	0.9	0.944	− 1.68
45	C-CRC-25R	4.4	0.0	232	236	1.0	0.984	− 0.47
46	C-CRC-15R	5.3	0.0	237	233	0.9	1.020	0.61
47	C-CRC-127R	5.7	0.0	228	224	0.9	1.018	0.54
48	C-CRC-15R	0.4	NR	233	226	0.9	1.033	1.00
49	C-CRC-15R	5.7	0.6	232	232	0.9	0.997	− 0.08
50	AN ACT-15P	5.3	NR	231	227	0.9	1.017	0.53
51	NA 34–164	3,8	0.9	184	223	0.9	0.827	− 5.25
52	AN ACT-15P	5.3	0.0	233	227	0.9	1.029	0.88
52*	V-AV-02	4.7	0.0	227	227	0.9	1.000	0.01

NR = Not reported.
*Means replication of the same sample in the same NMS measured in different time or different radionuclide calibrator: AN = Alfanuclear; C = Capintec; V = Vexcal; BMS = Biodex Medical System; FB = Fluke Biomedical; NA = Nuclear Associates.

30 less than 5%, 38 less than 10% and 4 differ more than 10%. Two NMSs did not return results. This indicates that 90% of the country's NMS has satisfactory results according to the norm (CNEN, 2013) which requires results to be within 10% of the true value.

The results that did not comply with the Brazilian norm were also considered not acceptable for the Z score ($|z| > 3$) since both criteria are related.

4. Discussion

Participants were very cooperative in the measurement and calculation steps of the bilateral program with IPEN and IRD.

The correction factor of 1.013 indicates the excellent quality of the calibration of the radionuclide calibrator used by IPEN to dispense the activities of radiopharmaceuticals requested by NMS in the country. This factor is lower than 2%, showing the measurement quality for ^{131}I to be consistent with IAEA-TRS454, for secondary traceability providers of radiopharmaceutical activity measurement in Nuclear Medicine (IAEA, 2006).

The consistency of the correction factors for the open and unopened samples reinforces the robustness of the method for rapid and accurate evaluation of the measurement of radiopharmaceutical activity in NMSs.

Associated with the cost factor, which in this case is much lower (radiopharmaceutical production and air shipping to destination cities), the method can be used on a large scale until calibration services traceable to LNMRI are deployed in the country.

The Brazilian norm just requires that the result is within 10% of the target value. It is now accepted elsewhere that uncertainties should also be taken into account but this requires all participants to become “expert” in estimating and combining uncertainties. It is clear from Table 1 that this is not yet the case. Many reported uncertainty values are smaller than the IPEN and IRD uncertainty values; a few are larger than would be expected. We are already discussing with participants how realistic uncertainty values can be produced and this is just for those who participated here. So it can be seen that this is a major task for all NMSs and cannot be achieved overnight.

Nevertheless this exercise has been invaluable in highlighting this problem.

It is also the case in Brazil that National Agency for Sanitary Surveillance (ANVISA) has norms which are more stringent and it is likely that these may be extended to NMSs in the future. This will be an added incentive for NMSs to develop their understanding and use of the uncertainties.

The experiences from this exercise also show that NMSs are more likely to participate in such comparisons if the comparison sources can be delivered to them rather than sending samples to IPEN.

The four results that do not comply with the Brazilian norm (CNEN, 2013) should be repeated at NMS after review of procedures.

5. Conclusions

This study demonstrated that the IPEN has traceability to IRD in the measurement of ^{131}I. In addition, having IRD as a reference, this is a fast and accurate tool for assessing the quality of ^{131}I measurements in NMSs.

The IPEN difference of measurement related to IRD for most radiopharmaceuticals distributed including ^{18}F is less than 2% (De Oliveira et al., 2016). With over 429 NMSs around the country, this study with ^{131}I confirms that this methodology allows the evaluation of the measurement conditions for radioactive sources with half-life equal or bigger then ^{18}F (provided on the same day).

Studies with other radiopharmaceuticals should be done to evaluate the measurement capacity and distribution infrastructure for the half-life lower than that of ^{131}I.

NMSs administrate medicine to the patients as radiopharmaceutical, for diagnosis or therapy. Therefore they must comply with norm for Good Manufacturing Practices (GMP), even though they don’t change the original formulation of the medicines.

The safe way to assure quality of activity measurement for NMSs in Brazil is participation in comparison programs. For this purpose, will need

1. Change in this already existing ANVISA's requirement (ANVISA, 2009) for Radiopharmaceutical Producer Center (RPC), that needs to be extended to NMSs.
2. IRD must continue offering quality control program with certificate accepted by ANVISA as follows:
   a. Directly or as defined at the present work, using a RPC with excellent traceability;
   b. Evaluating NMSs Performance in accordance with National Standard using a calibration service traceable to IRD. The first of these is now being certified by IRD;
   c. Creating more REGLABs in the country. As they have traceability to IRD, can act as calibration service or run an itinerant quality control program.

This exercise has shown that successful comparison programs can be conducted which could cover the entire country.

This study has also highlighted the need to provide training and advice in the estimation and application of uncertainties.

Acknowledgement

The authors would like to acknowledge the advice and encouragement given by the other partners in ARCAL RLA 6074, namely P. Oropesa Verdecia, P. A Arenillas, Oyarzun C. H., García L., Guardo C., Moreno Y. We appreciate the cooperation of the participating NMSs. Also, all the support given by CNEN’ staff (headquarter, REGLABs, IPEN and IRD), on importing and shipping of sources, preparing samples, and others necessary actions.

References

ANVISA, 2009. Resolução-RDC no. 63, de 18 de Dezembro de 2009. Provides for Good Pharmaceutical Manufacturing Practice (in Portuguese).

ARCAL, 2016. Oropesa, P., Arenillas, P., De Oliveira, A.E., et al., 2016. Relato Técnico Final del ejercicio de comparación de las mediciones de la actividad de radionúclidos terapéuticos con activímetros en América Latina y el Caribe ARCAL 6074/- Agencia Internacional de Energía Atómica.

CNEN, 2013. National Nuclear Energy Commission: Requirements of Radiation-Protection and Safety for Nuclear Medicine Services. Norm CNEN NN- 3.05 (in Portuguese).

De Oliveira, A.E., Iwahara, A., da Silva, C.J., et al., 2016. Traceability from governmental producers of radiopharmaceuticals in measuring ^{18}F in Brazil. Appl. Radiat. Isot. 109, 236–241.

IAEA, 2006. Technical Report Series TRS454 – Radioactivity Measurement for Quality Assurance in Nuclear Medicine in Nuclear Medicine.

ISO/IEC 17043, 2011. Conformity Assessment – General Requirements for Proficiency Testing.

Rosario, P., Martínez, J.L., Silván, J.M., 2007. Evaluation of Proficiency Test Data by Different Statistical Methods Comparison. The First International Proficiency Testing Conference. Sinaia, Romania 11–13 October, 2007.

Schrader, H., 1997. Activity measurements with ionization chambers Monograph BIPM-4 (Sevres, France: International Bureau of Poids and Mesures), p. 176.