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The Support Offered by the Romanian Primary Activity Standard Laboratory to the Nuclear Medicine Field

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Abstract

The paper presents the following aspects of the involvement of the Radionuclide Metrology Laboratory from IFIN-HH, Romania, in the assurance of the correct measurement of radiopharmaceuticals activity in nuclear medicine, as well as in production and control units: development and international validation of primary standards, development of secondary standards and direct support offered to the domain, consisting from calibration services and organization of comparisons/proficiency tests. A detailed analysis of the results obtained in the calibration of several types of radionuclide calibrators during a six years period is presented. It includes the following actions: check of the measurement uncertainty, recalibration when necessary, control of the calibrators' behavior in time; a comparison between calibration check and the results of the participation of the staff at proficiency tests is also done.

Key words: *radiopharmaceutical product, primary activity standard, International System of Units (SI), radionuclide calibrator, metrology services*

1. Introduction

The quality of a nuclear medicine procedure depends on the activity and quality of the radiopharmaceutical administrated, *IAEA-TRS 454* [1]. Both aspects are connected with high precision measurement of activity (Becquerel) and derived units. The technical support is offered by the Primary Activity Standard Laboratories, like the Radionuclide Metrology Laboratory (RML) from IFIN-HH, which assures the continuity of the whole metrological traceability chain of measurement. The RML's role is [2]: to develop activity standards, to validate them in relation with the International System (SI) and to disseminate them as radioactive standards, or calibration services. The paper presents RML's actions and results. (i) Development of installations and methods for the primary/absolute standardization of radionuclides: a coincidence installation with two detection blocks and a liquid scintillation counte, triple to double coincidence ratio (LSC-TDCR) system. They were internationally validated, through key or supplementary BIPM comparisons, and their international equivalence was established. RML's results are part of *the Key Comparison Data Base (KCDB) Annex B of the CIPM – MRA*. The supplementary comparisons, within the IAEA-CRP E2.10.05, regarded ^{57}Co and ^{131}I. Implementation of the Quality Management System (QMS), in accordance with the standard EN ISO/IEC 17025:2005 and its recognition by the EURAMET TC-Q, allowed the approval and publication of RML's 34 Calibration and Measurement Capability (CMC) files in the Annex C of the CIPM-MRA. (ii) Establishment of a

secondary standard, reentrant ionization chamber CENTRONIC IG12/20A, calibrated and validated for 20 radionuclides. The determined calibration factors allow the measurement and certification of the radiopharmaceutical standards. (iii) The direct support of RML to the nuclear medicine units consists from: delivery of radioactive standards; calibration or metrological check of the Radionuclide Calibrators; organization of national comparisons and proficiency tests (PTs). These actions are deployed under the Laboratory's national RENAR (EA member) accreditation, as a Calibration and Testing Laboratory, for the products and services for clients. The description of the calibration services for radionuclide calibrators presents a 6-years work period, in the following aspects: check of the measurement uncertainty and comparison with Pharmacopoeia requirements; recalibration and establishment of new calibration factors (dial settings); follow up of the calibrator's behavior in time; comparison of the activity values measured with the most used instruments: Curiementor 3 and 3/4, Capintec CRC 15/25R, Romanian EMR 15G instrument, Picker, with the reference value; results of calibration check versus the participation of nuclear medicine staff at Proficiency Tests (PTs) organized by the RML. Some conclusions and recommendations are formulated.

2. Radioactive standards for nuclear medicine realized in the RML and their validation through international comparisons

The Radionuclide Metrology Laboratory from IFIN-HH, in its quality of designated, primary standard laboratory in the field of radionuclide measurement, has as main objective the construction of installations and elaboration of methods for absolute standardization of a large number of radionuclides, for various applications, the nuclear medicine being among the most important. The number and the variety of decay schemes of the medical radionuclides required the setting of three types of installations to be used in the standardization: (i) the classical coincidence installation and method, based on a 4π proportional counter (PC) type pill box, and a NaI(Tl) detector, working in coincidence, the $4\pi\beta$(PC)-γ system; (ii) a coincidence detection block containing two thin NaI(Tl) detectors for the registration of x-x,γ coincidences; (iii) a liquid scintillation counter, based on the method of triple to double coincidence ratio (LSC-TDCR), containing alternatively a set of three photomultipliers or a set of six channel photomultipliers, and a coincidence counting system. They practically cover the necessity for absolute standardization of all medical radionuclides used for diagnostic and targeted therapy, which differ essentially regarding the decay scheme and types of emitted radiations.

In the field of diagnostic, the most used radiopharmaceuticals in Romania are based on the radionuclides: ^{99m}Tc, ^{131}I for SPET and ^{18}F used in the new PET/CT systems. In this last case, an important role will play also the radionuclides ^{64}Cu and ^{68}Ga, which are under study. In the field of therapy, the most used radionuclide is ^{131}I, followed by ^{32}P, ^{89}Sr, ^{90}Y. The radionuclides: ^{153}Sm, ^{177}Lu, ^{186}Re and ^{188}Re are under study at the radiopharmaceutical unit from IFIN-HH. A special situation has the radionuclide ^{125}I, which is used for both radiodiagnostic in RadioImmunoAssay (RIA) analysis and its derived techniques, and in therapy for brachytherapy and for the targeted therapy with Auger electrons emitters. All these radionuclides were absolutely standardized in LMR. A short description of their standardization and validation in relation with the International System of Units (SI) is presented.

Radionuclide ^{99m}Tc decays by an isomer transition to the ground state of ^{99}Tc, with the emission of the 140.5 keV (89%) radiations, used for the SPET investigation. It also emits K x-rays in the interval (18.25 - 21.01) keV and conversion electrons of 2.13 keV and (119.5 - 142) keV. It was standardized in RML by an original coincidence method, based on the coincidences between (119.5 – 142.6) keV

conversion electrons and the K x-rays [3]. Alternatively it was measured by the gamma ray spectrometry with a calibrated spectrometer, the agreement of the methods being very good. Due to its short half life, 6.007 h, the international validation was possible only through the participation in the supplementary comparison *"CCRI(II)-S6.Co-57*" organized within the International Atomic Energy Agency (IAEA) Coordinated Research Project (CRP) codified as: E2.10.05, entitled: *"Harmonization of quality practices for nuclear medicine radioactivity measurements*". The results are presented in the paper [4]. Two CMC files, for two levels of activity, were transmitted to the EURAMET and are under inter-regional metrology organizations' analysis.

Radionuclide ^{131}I decays by beta – gamma ray emission. It was standardized absolutely in LMR by using the 4πβ(PC)-γ coincidence method in the variant of efficiency extrapolation, with the assurance of the linearity conditions, such as presented in the paper [5]. The validation of the method was realized by the participation at two international comparisons: the key comparison type *"BIPM(RII)-K1",* within the International Reference System (SIR), as presented in the paper [6], and the *Key Comparison Data Base (KCDB) Annex B of the CIPM – MRA*, which can be found at the address: http://kcdb.bipm.org/AppendixB/KCDB_ApB_search.asp, and also the participation at the supplementary comparison *"CCRI(II)-S6.I-131*" whose results are reflected in the paper [7]. On this basis, two CMC files of the radionuclide were approved and included in *the Annex C- Calibration and Measurement Capabilities (CMC), of the CIPM-MRA.*

Radionuclide^{18}F, a positron emitting radionuclide, was not yet standardized, but it is planned for the next future. Two other positron emitters, used in PET systems, were already absolutely standardized**: ^{64}Cu,** within the EURAMET project 1085, and **^{68}Ga**. Both of them decay by a combination of beta decays and electron capture, having complex decay schemes. Usually, they are standardized in different laboratories by using the coincidence method with the counting of coincidences between the positrons and 511 keV-annihilation quanta [8 - 10]. It was noticed that both radionuclides have similarities in the decay scheme configuration and a new method, based on the coincidences between positrons and x-ray Auger electrons with the annihilation quanta and high energy gamma rays was used for their standardization. The measurement results were compared with those obtained by applying the classical, positron-annihilation quanta coincidences and with the gamma-ray spectrometry method. The results are presented in the paper [11]. No international comparison was possible up to now, due to the short half lives of radionuclides, 12.70 h and respectively 1.127 h.

Radionuclides ^{32}P, ^{89}Sr, ^{90}Y, used for targeted therapy, are all of them pure beta emitters, with the emission of high energy beta rays. For the radionuclides ^{32}P and ^{89}Sr, the LSC-TDCR method and system were applied in standardization. In the case of ^{32}P we participated at the key comparison "*CCRI(II)-K2.P-32*". The result was less satisfactory, due to the impurification of the solution with ^{33}P and ^{35}S, lower energy pure beta emitters, for which the determination of activities and their extraction from the activity of ^{32}P was affected of high uncertainties. In the case of ^{89}Sr, the standardization was done within the key comparison "*CCRI(II)-K2.Sr-89*". Two parallel methods were applied: the LSC-TDCR and the alternative method of the tracer efficiency, with the use of a ^{60}Co standard solution as tracer [12, 13]. The results of the comparison will be soon published by the BIPM.

In the case of ^{90}Y we measured the more complex ^{90}(Sr+Y) decay chain by the LSC-TDCR method and compared the obtained results with the classical system, based on the use of three photomultipliers, with those for the new detection block constructed in the laboratory, consisting from six

channel photomultipliers (CPMs). The good agreement of the two results, with a difference of maximum 1%, validates the measurement method [14].

Radionuclides ^{153}Sm, ^{177}Lu, ^{186}Re and ^{188}Re are strong beta and weak gamma-ray emitters, with important transitions to the ground level of the daughters, belonging to the category of the so called "triangular decay scheme". All of them were standardized by the 4πβ(PC)-γ coincidence method in the variant of efficiency extrapolation, specially adapted for this kind of decay scheme. The results were published in the papers [15 - 17]. In the case of ^{177}Lu, with a longer half life of 6.71 d, we participated at the key comparison "*CCRI(II)-K2.Lu-177*", whose results were published in the paper [18].

Radionuclide ^{125}I decays by electron capture process, with the emission of Auger electrons of (2.3 – 4.8) keV and (21.8- 31.8) keV, conversion electrons of 3.7 keV and (30.6 – 35.5) keV, x-rays of (27.2 – 31.7) keV and gamma rays of 35.49 keV. Its standardization is done by the use of sum-peak method or the x-x,γ coincidence. Both methods were used in LMR. The sum-peak method was affected by large uncertainties, due to the corrections to be applied, what influenced the result obtained in the key-comparison "*CCRI(II)-K.2I-125*". After the setting of the new coincidence block, the coincidence method was applied [19]. In order to verify the results, we realized a link between the coincidence measurements and key comparison result via the calibration of the Multi-gamma counter type LKB 2104, provided with 12 well type NaI(Tl) crystals, 1,1/8″ x 1,1/8″ , belonging to the Radioimmunoassay (RIA) Laboratory from IFIN-HH. A difference of only 1.8% between the coincidence measured solution and the key comparison reference value was found, such as is presented in the paper [20].

A general conclusion of the chapter is that the Radionuclide Metrology Laboratory can assure the national traceability of measurements in nuclear medicine for all radionuclides being used.

3. Establishment of the secondary standard, reentrant ionization chamber CENTRONIC IG12/20A

The ionization chamber is known to be a very stable instrument, able to keep the calibration factors values for many years. The stability is maintained in terms of less than 0.01 % long term variation of the indication for a ^{137}Cs standard source, which is measured at the beginning of each calibration. Our ionization chamber was calibrated for a long list of gamma-ray emitting radionuclides, the most recent being ^{64}Cu and ^{68}Ga. The initial electrometric system consisted of an NP 2000 electrometer, supplied by MKEH (former OMH, Hungary) and a set of four capacitors, in decades, from 0.1 nF up to 100 nF and the measurement of the decay rate of the capacitor versus activity. The calibration factor was expressed in (V s^{-1})/MBq, specific for each radionuclide; for each activity interval it was necessary to use a different capacitor [21]. More recently, the electrometric system was replaced with a Keithley 6517A electrometer, allowing the direct calibration in terms of pA/MBq, used for the entire measured activity interval. The calibration was done for various types of recipients, as follows: ampoules with 2 mL (PTB-Germany), 3.6 mL (SIR) and 5 mL vials (P6, penicillin), of standard solution. In order to keep the old calibrations, it was necessary to determine very precisely the old capacitors' values, and to convert the units (V s^{-1})/MBq to pA/MBq. The validation of the calibration factors was done via the comparisons conducted through the CIPM-MRA comparison route, Appendix B of the BIPM KCDB database (http://kcdb.bipm.org/AppendixB/KCDB_ApB_search.asp). Another validation consisted from the comparison of results with those obtained in 2001, when the chamber was calibrated at Physikalisch Technische Bundesanstalt (PTB), Braunschweig, Germany [22] for 18 radionuclides, using PTB standard solutions in 2 mL vials. The values of the calibration factors are presented in the papers [11, 23]

4. Support of RML to the nuclear medicine: delivery of radioactive standards and metrology services

The Radionuclide Metrology Laboratory prepares all kinds of radioactive standards for the nuclear medicine units. The direct delivery is done mainly within the frame of the comparisons and

proficiency tests. The solutions or ^{131}I capsules are prepared and calibrated in the laboratory for each operation performed for external users.

The most important operation is the calibration of the Radionuclide Calibrators belonging to the IFIN-HH Radiopharmaceutical unit, to the National Agency for Drug Control and to the Nuclear Medicine units; the legal metrological check was mandatory only before the year 2010.

At the same time, several rounds of national comparisons regarding the radionuclides ^{131}I, ^{57}Co and ^{99m}Tc were organized. The last ones, ^{131}I in 2007 and ^{99m}Tc in 2008, were organized within the frame of the IAEA – CRP E2.10.05:*"Harmonization of quality practices for nuclear medicine radioactivity measurements*" and the results are published in the papers [24 - 26]. The presented data were expressed as ratios:

$$R = A_{meas} / A_{c.a.} \quad (1)$$

A_{meas} is the activity measured and reported by the participants at the comparisons and $A_{c.a.}$ is the conventionally true activity, certified by the RML, with expanded uncertainties of 1.5 % for ^{131}I and 3.0 % for ^{99m}Tc, corresponding to a coverage factor $k = 2$ (95 % confidence level).

In the case of ^{131}I, the ratio's values were $0.851 \leq R \leq 1.383$, with 80 % of the 12 results being compliant with the Pharmacopoeia requirement of maximum 10% measurement uncertainty. In the case of ^{99m}Tc, $0.954 \leq R \leq 1.077$, with 100% of the 7 results being compliant.

As it can be seen from the presented data, the calibration in our laboratory of the radionuclide calibrators belonging to the users proved to be necessary, in order to assure the correct calibration of the instruments and to establish if the wrong results in comparisons are due to the calibrators or to the human errors in radiopharmaceuticals measurement. The calibrations were performed in the regime of accreditation of the laboratory for calibration by the Romanian accreditation body, RENAR, and notification by the National Nuclear Authority, CNCAN, according to the EN ISO/IEC 17025:2005*"General Requirements for the Competence of Testing and Calibration Laboratories"*. A special work procedure, codified as AC-PL-LMR-11, was written and followed.

4.1 Calibration operations to be performed.

(i) Measurement of the background indication and ionization chamber decontamination, if necessary. In some cases the value is automatically subtracted from measurement, in others it is subtracted during the calibration operation.
(ii) Preparation and calibration of standard solution, with the volume of 5 ml, contained in a P6 vial, or of standard gelatin ^{131}I capsules, using the secondary standard, CENTRONIC IG12/20A ionization chamber.
(iii) Calibration, consisting in the following steps. Measurement of the standard solution, or capsules, with the radionuclide calibrator. Two situations can occur: (a) The difference from reference activity is higher than ± 10 % and then the calibration factor (dial setting) is modified until the difference is conform; the new dial setting is written in the certificate and is strongly recommended to be used in measurements at the hospital. When the adjustment is not possible, the value of the correction factor to be applied to the measurement result is written in the certificate. (b) The obtained value differs from the conventionally true one by less than ± 10 %, and, in this case, both values are written in the calibration certificate. In many cases, the original calibration factor was reconfirmed, mainly before 2009. In majority of the cases, the ratio R was calculated according to relation (1) where A_{meas} is the activity measured with the apparatus to be calibrated, such as it is presented further in the paper. The uncertainty of ratios was calculated combining the values: 1.5% for ^{99m}Tc and 0.75 % for ^{131}I (k = 1) with the values declared in the technical documentation of instruments, 5 %.
(iv) Follow up of the decay of the standard solution, by more than 24 h, in order to verify the linearity of response on more than one decade of activities variation.
(v) Follow up an apparatus behavior for several years of utilization.
(vi) Check of ^{99}Mo breakthrough in ^{99m}Tc.

4.2 Results obtained in calibration.

(iii a) The dial setting modification was done in two cases. One refers to some calibrators type Picker, purchased by hospitals many years ago, which had to be used further for measurements. The adjustments of the dial settings were both positive and negative. Two examples are relevant: for one calibrator, the ratio R obtained at the measurement of a ^{131}I solution was found as: R = 0.786 (P6 vial). After the adjustment, the new value was found as R = 0.998; for another apparatus, in the case of a ^{99m}Tc solution measurement, the respective values were: R = 1.120 and respectively R = 0.998. Another case is represented by old Curiementor 2 and 3 calibrators. In the case of Curiementor 2, when measuring ^{131}I solution an initial value of R = 0.851 was obtained, and after adjustment it became R = 0.996. In the case of two Curiementor 3 instruments, the value was R = 0.870 and consequently an amplification factor f = (1.15 ± 0.03) was recommended.
(iii b) All cases refer to the differences less than ± 10 %. Table 1 reflects the obtained results.

Table 1 Values of the ratio R obtained with various calibrators

Year of calibration	Type of calibrator	R , ^{99m}Tc	R , ^{131}I
2006	Capintec CRC-15 R/1	-	0.999 ± 0.051 solution
	Capintec CRC-15 R/2	-	1.005 ± 0.051 solution
2007	Curiementor 3	adjustment	-
2008	Various types	calibration confirmed	calibration confirmed
2009	Curiementor 3	adjustment	-
	Curiementor 3	0.913 ± 0.050	-
	EMR-15 G	0.979 ± 0.052	-
	Curiementor 3	0.966 ± 0.052	-
	Capintec CRC-15 R/1	-	1.004 ± 0.051capsules
	Capintec CRC-15 R/2	-	0.989 ± 0.051capsules
	Curiementor 3	0.964 ± 0.052	0.960 ± 0.051solution
	Picker MicroCal	0.987 ± 0.052	0.972 ± 0.051solution
2010	Capintec CRC-15 R	-	1.009 ± 0.051solution 1.025 ± 0.051capsules
	Curiementor 3	0.958 ± 0.052	0.971 ± 0.051 capsules
	Curiementor 3	1.008 ± 0.052	0.979 ± 0.051 capsules
	Curiementor 3	0.969 ± 0.052	0.985 ± 0.051 capsules

	Picker	adjustment	-
2011	Curiementor ¾	0.974 ± 0.052	-
	Curiementor 3	0.937 ± 0.052	-
	Curiementor ¾	0.961 ± 0.052	-
	Capintec CRC-25 R	1.030 ± 0.052	-
	Capintec CRC-15 R	-	1.003 ± 0.051solution 1.020 ± 0.051capsules
	Capintec CRC-15 R	-	1.009 ± 0.051solution
	Picker	-	1.039 ± 0.051solution 1.017 ±0.051capsules
	Curiementor ¾	0.963 ± 0.052	-
	Robotron M 27013	1.039 ± 0.052	0.957 ± 0.051solution
	Curiementor 3	0.970 ± 0.052	0.972 ± 0.051 solution
	Curiementor 3	0.976 ± 0.052	0.972 ± 0.051 solution
	EMR 15G	0.992 ± 0.052	-
	Capintec CRC-15 R	1.032 ± 0.052	-
	Curiementor 3	0.968 ± 0.052	-
Mean ratios	**Curiementor 3 and ¾**	**0.964 ± 0.022**	**0.973 ± 0.008**
	CRC-15 R and 25 R	**1.031 ± 0.001**	**1.008 ± 0.012**
	Picker and Picker MicroCal	**0.993 ± 0.006**	**1.009 ± 0.034**
Mean ratio	**All calibrators**	**0.978 ± 0.032**	**0.995 ± 0.023**

Discussion of Table 1 results.From the calculation of the mean ratios one may conclude: All the calibrators, except two Curiementor 3 units, ^{99m}Tc, differ by less than (- 5 %) from the reference value, conventionally true activity. Regarding the ^{99m}Tc calibration: The Curiementor calibration is (- 3.6 %) different from the reference, while the Capintec calibration is (+ 3.1 %), what means that the measurements of the same recipient with solution with the two types of instruments differ by 6.6 %; the Picker calibration is different by (- 0.7 %). Regarding ^{131}I, the respective calibrations are (- 2.7 %) for Curiementor and (+ 0.8 %) for Capintec; the Picker calibration difference is (+ 0.9 %). The mean ratio of all Calibrators is in agreement with the reference value, within the standard uncertainty.

(iv) Linearity test, performed by the follow up of the decay. All the calibrators are followed for ^{99m}Tc decay during a 24 h interval. Table 2 presents the values of the ratio *R* between the measured and calculated activity for both the main types, Curiementor 3 and Capintec 15 R calibrators.

Table 2. Linearity check of calibrators

Activity, MBq	1400	1225	972	97	76
R Curiementor 3	1.0000	0.9974	1.0036	1.0014	1.0010
R Capintec CRC 15R	1.0000	1.0008	1.0002	0.9968	1.0041

From Table 2 one may conclude that the linearity is satisfactory enough, for activities from 70 MBq up to 1400 MBq, the differences from the calculated and measured activities being in all cases less than 0.5 %.
(v) Follow up of one apparatus during several years of utilization. A systematic study was possible with the Capintec 15 R calibrators belonging to the IFIN-HH radiopharmaceutical unit. Table 3 presents the results for the measurement of ^{131}I solution and capsules, in terms of ratio between measured and reference activity.

Table 3.Long term behavior, ^{131}I measurement

Year/ *R* value	2006	2009	2010	2011
Capintec CRC-15 R/1	0.999 ± 0.051 solution	1.004 ± 0.051 capsules	1.003 ± 0.051 solution 1.020 ± 0.051 capsules	1.003 ± 0.051 solution 1.020 ± 0.051 capsules
Capintec CRC-15 R/2	1.005 ± 0.051 solution	0.989 ± 0.051 capsules	1.009 ± 0.051 solution	1.009 ± 0.051 solution

From Table 3 one concludes that in the case of solution measurement, the stability is better than 0.9 %, with no trend in indication variation, while for capsules measurement it can reach maximum 2 %.
(vi) Regarding the check of the measurement of ^{99}Mo breakthrough (radionuclide ^{99m}Tc purity), only a few calibrators are provided with the lead shield for this operation. In all cases it was measured and it was found a ^{99}Mo content in the solution less than 0.001 from ^{99m}Tc activity, conform with the pharmacopoeia requirement, radionuclide purity better that 99.9 %.

5. Conclusions

- The paper presents all aspects of the support given by the Radionuclide Metrology Laboratory from IFIN-HH to the Romanian units involved in nuclear medicine, in order to assure the whole metrological traceability chain, from the SI up to the end users.
- The most relevant direct support offered to the end users consisted in the metrological operation of calibration of radionuclide calibrators.
- One may conclude that every year the operation was amplified in volume and new, high quality, instruments were purchased by the nuclear medicine units.
- With some exceptions, the majority of calibrators' indication differs by less than ± 5 % of the reference activities, certified by RML; the erroneous results obtained in comparisons are mainly due to the human errors in measurement.

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