

QUALITY ASSURANCE IN NUCLEAR MEDICINE RADIOACTIVITY MEASUREMENTS

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Abstract. The paper presents some recent results of the Radionuclide Metrology Laboratory (RML) from IFIN-HH, in the assurance of quality in radioactivity measurements for nuclear medicine. Three aspects are treated: (i) Participation of the RML in the frame of the IAEA Coordinated Research Program (CRP), E 2.10.05; (ii) Improvement of the secondary standard, based on a CENTRONIC IG12/20A ionization chamber; (iii) Implementation of the quality management, according to the SR EN ISO/IEC 17025:2005.

Key words: nuclear medicine, quality assurance, key comparison, calibration.

1. INTRODUCTION

The tradition of radiopharmaceutical production in the Radioisotope Research – Production Center (CPR) of IFIN-HH, to be used in Romanian nuclear medicine units, is longer than 40 years. The concern of the Center for purchasing conventional equipment and developing relative measurement methods was in connection with the correct measurement of radiometrological, and physico-chemical parameters, in production, legal distribution and use of the radiopharmaceuticals. The metrological traceability chain at a primary radioactivity standard had to be established, too. The accomplishment of this requirement was possible as the Radionuclide Metrology Laboratory (RML), the primary Romanian radioactivity standard, is situated in the structure of CPR, very near the practical measurement necessities. At the same time, being connected at the metrology international and national network, RML was able to solve successfully all these tasks. The paper presents the most recent results in the field, concentrated in three basic directions:

(i) Participation of the RML in the frame of the IAEA Coordinated Research Program (CRP): E 2.10.05 “Harmonization of quality practices for nuclear medicine radioactivity measurements”, Project: “Assurance of the traceability

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chain between IAEA, IFIN-HH – RML, and end-users – Romanian hospitals, for nuclear medicine radioactivity measurements”;

(ii) Improvement of the secondary standard, based on a CENTRONIC IG12/20A ionization chamber, by the use of a highest quality electrometer, type Keithley E6517A, and transfer of the calibration figures to the new system;

(iii) Implementation of the quality management, according to the SR EN ISO/IEC 17025:2005 “General requirements for the competence of testing and calibration laboratories” in radioactivity measurement.

2. IAEA CRP E 2.10.05 PARTICIPATION

The RML developed methods of absolute standardization for main part of radionuclides used in nuclear medicine, well recognized at the international level. This was the reason for which a member of the laboratory was asked to participate in a Consultants Meeting, 02CT10614, “Methodology for Radioactivity Standardization”, held in Vienna during 2002, which advised for the development of a set of procedures in the form of a draft Code of Practice (CoP) for radioactivity measurement practices and the configuration of a Quality Assurance scheme. The participants were: Dr. Brian E. Zimmerman, National Institute of Standards and Technology (NIST), Gaithersburg, MD, USA, an expert in radionuclide metrology; Dr. Maria Sahagia, National Institute of R&D for Physics and Nuclear Engineering “Horia Hulubei” (IFIN-HH), Bucharest, Romania, an expert in radionuclide metrology; Dr. Michael G. Stabin, Vanderbilt University, Nashville, TN, USA, an expert in internal dosimetry for nuclear medicine applications. A new Consultant’s Meeting 04CT07684, “Harmonization of Quality Assurance Practices for Nuclear Medicine Radioactivity Measurements” was kept in Vienna during 2004, with the participation of: Dr. Brian Zimmerman, representing IAEA, DMRP-NAHU; Dr. Charles Herbst (SAF), Department of Medical Physics, University of the Free State, Bloemfontein; Prof. Jeffrey Norenberg (USA), University of New Mexico School of Pharmacy, Mr. Michael Woods (UK), Ionising Radiation Metrology Consultants, Ltd. an expert in the field of radionuclide metrology.

As a conclusion of the above actions, it was decided at the IAEA level to initiate a new Coordinated Research Project, devoted to elaborate the Quality Assurance (QA) documents and to help the practical implementation of the Quality System (QS) in nuclear medicine measurements. The result was the initiation of the CRP:E 2.10.05 “Harmonization of quality practices for nuclear medicine radioactivity measurements”. Our laboratory is involved in the Romanian Project: “Assurance of the traceability chain between IAEA, IFIN-HH – RML, and end-users – Romanian hospitals, for nuclear medicine radioactivity measurements” was concluded as an IFIN-HH contract. The work carried out implied several actions, according to the objectives of the contract.

2.1. WORK AT THE FIRST RESEARCH COORDINATED MEETING

(i) A report and a work program draft, presented at the 1st, RCM of the CRP E2.10.05, reflected the following aspects: The present situation of radioactivity measurements in nuclear medicine in Romania; the applicable legislation for the measurement of activity; accreditation bodies and applicable documents; the role of the Radionuclide Metrology Laboratory from IFIN-HH in nuclear medicine measurements.

(ii) The common work, developed together with the other participants in the CRP, aimed to define the next future deployment of the Project, and contributed to the issue of the Document: International Atomic Energy Agency (IAEA) – Vienna, Austria – Technical Report Series 454 (TRS 454), 2006, “Quality Assurance for Radioactivity Measurements in Nuclear Medicine” pp. 1–96, ISBN 92-0-105306-1, ISSN 0074-1914, Contributors to drafting and review: M. Dondi, C. P. Herbst, A. Iwahara, M. Morengo, S. Mather, J. P. Norenberg, V. Olsovcova, P. Oropesa Verdecia, P. Otiz-Lopez, L. Joseph, M. Ghafoori, J. A. Onto, N. Ramamoorthy, M. Sahagia, K. R. Shortt, S. Tasthan, P. Vincze, M. J. Woods, B. E. Zimmerman.

(iii) Absolute standardization of Tc-99m and Lu-177; transfer of calibration figures for CENTRONIC ionization chamber and for hospitals in Romania.

The radionuclides ^{99m}Tc and ^{177}Lu were prepared as radioactive solutions, which were absolutely standardized, by using the $4\pi\text{PC} -\gamma$ coincidence method. The secondary standard of the Radionuclide Metrology Laboratory, ionization chamber CENTRONIC IG12/20A, was calibrated for the two radionuclides. In the case of ^{99m}Tc , the calibration factor uncertainty was calculated as $u_c = 2\%$ ($k = 1$). The agreement of the newly determined value with the calibration factor established at PTB-Germany, for the same chamber, was within the limit of 0.66%. The calibration was transferred to the hospitals during the metrological checks performed with radioisotope calibrators. In the case of ^{177}Lu , two absolute standardizations and consequently two calibrations were made. The mean value of the calibration factor was assigned to the chamber, and the final uncertainty was reported as $u_c = 1.1\%$ ($k = 1$). The calibration figures were transferred to the commercial calibrators used in the radioisotope Department, as the hospitals do not use ^{177}Lu , yet. The results were already published [1–4].

2.2. SIR BIPM-RI(II).K1.I-131, KEY COMPARISON AND CALIBRATION OF THE IONIZATION CHAMBER

(i) As a primary standardization laboratory, the effort was devoted to the assurance of the traceability chain for ^{131}I activity measurement. We participated at a key comparison, within the frame of the International Committee for Weights and

Measures – Mutual Recognition Arrangement (CIPM-MRA), by the International Reference System (SIR), the key comparison code BIPM-RI(II).K1.I-131. The standardization method was described in a paper sent for publication [5]. Combined uncertainty of the reported radioactive concentration, according to GUM [6], is $u_c = 0.29\%$, ($k = 1$).

(ii) New calibration of the Ionisation chamber CENTRONIC IG12/20A.

The second action was to perform a new calibration of the Ionisation Chamber CENTRONIC IG12/20A for ^{131}I : The ionisation chamber was calibrated during the SIR comparison, by using the vials with standard solution. The activity values, A, MBq, were calculated by multiplying the activity concentration, BIPM reported, by the mass of solution in the vials and applying decay corrections for the measurement date. The calibration was performed for various types of vials, and uncertainties were evaluated. The procedure and results are largely described in the paper [5], too. They are in good agreement with those obtained during a previous calibration of the chamber at PTB, Braunschweig, Germany [7], a difference between results, $U = 0.88\%$ being reported.

2.3. PARTICIPATION IN THE I-131 COMPARISON, IAEA, 2006, CRP E.2.10.05

According to the work programme of the CRP E 2.10.05, our Laboratory participated at the comparison for a I-131 solution, and the results were submitted to the organizer of the comparison, the Dosimetry and Medical Radiation Physics Section, IAEA, on July 18, 2006, according to: Draft protocol for performing radioactivity measurement comparisons with Secondary Standard Dosimetry (Radioactivity) Laboratories [SSD(R)Ls], elaborated during the IAEA- RCM. The reference standard solution, as a blind sample, was supplied by the QSA GLOBAL, Germany. The RML reported activity of the solution in the original vial, for the comparison date, had an uncertainty: $u_A = 0.35\%$ ($k = 1$); a separate, detailed list, accounting for the uncertainty budget, agreed in the Draft protocol for SSDL comparisons was also completed. Late 2006, the Standardization Certificate issued by the QSA GLOBAL, reported the reference value, assigned by the supplier, with the extended uncertainty $U_A = 3.0\%$ ($k = 2$), respectively $u_A = 1.5\%$ ($k = 1$).

The comparison of results, emphasized that the IFIN-HH result is situated between the two comparative results, being -0.73% lower than the corresponding result by the use of PTB calibration [7] and $+1.74\%$ higher than the QSA GLOBAL certified value. A paper, intended to present the comparison and its results, is proposed for presentation at the 16-th International Conference on Radionuclide Metrology and its Applications, ICRM 2007, Capetown, South Africa, September 3–7, 2007, by the IAEA organizer staff [8].

The comparison was considered as being relevant for international equivalence system and was included in the Key Comparison Data Base of the CIPM-MRA, as a Supplementary key comparison, code CCRI(II)-S6.I-131/2006.

3. IMPROVEMENT OF THE SECONDARY STANDARD

The secondary standard, based on a CENTRONIC IG12/20A ionization chamber, was improved by the use of a highest quality electrometer, type Keithley E6517A and transfer of the calibration figures to the new system, which was put into operation in parallel with the old electrometric system. Preliminary measurements, by using the IAEA comparison I-131 vials prepared in Laboratory, in order to transfer the calibration figures, from F units, [MBq/(V/s)], which were previously determined for a number of radionuclides, to ionization current units, F1, [pA/MBq], were performed. They were used to calculate precisely the capacitors values, and to perform a correct transfer of calibration figures. Some preliminary, parallel registrations, of the discharge rates, and ionization currents, calculated for the same radioactive solution and same measurement date and hour, allowed for calculation of the capacitors values of the old electrometric system as the ratio between the ionization current measured with the electrometer Keithley, I [nA] and the discharge rate of the capacitor, D [V/s] $C = I/D$, [nA/(V/s)] = [nF], C represent some preliminary determined capacitor values, such as presented in Table 1. By further determinations of the capacitor values, the uncertainty in capacitor values will be lowered and the transfer of the previous response factors, F[MBq/(V/s)], will be converted into new calibration factors, F1 [pA/MBq] for various radionuclides.

Table 1

Correspondence between the old, F, and new, F1, transferred calibration factors of the ionization chamber and capacitor values

Vial type	Activity, on measurement date A [MBq]	Discharge rate, D [V/s]	Ionization current, I [pA]	F = A/D [MBq/(V/s)]	F1 = I/A, [pA/MBq]	Capacity C [nF]
SIR, 3.6 mL	98.30 ± 0.34 (0.35%)	1.2666 ± 0.0013 (0.1%)	1274.3 ± 2.7 (0.21%)	77.61 ± 0.28 (0.36%)	12.963 ± 0.053 (0.41%)	1.006 ± 0.0022 (0.21%)
PTB, 2.0 mL	70.36 ± 0.25 (0.35%)	0.9124 ± 0.0009 (0.1%)	919.76 ± 0.14 (0.015%)	77.12 ± 0.28 (0.36%)	13.072 ± 0.046 (0.35%)	1.008 ± 0.001 (0.1%)

From the above preliminary results, one may conclude that the transfer of calibration factor is possible, but further supplementary measurements are still necessary. The capacitor determined values must be improved, by the use of other radionuclides and a large interval of ionization currents.

4. IMPLEMENTATION OF THE QUALITY MANAGEMENT SYSTEM

4.1 AUTHORIZED ACTIVITIES

The laboratory deploys authorized activities, for which the renewal of authorizations was recently obtained:

(i) Renewal of the Authorization for legal metrology activities in the regulated field of equipment for activity measurement: “Ionization chamber installations for gamma nuclides activity measurement”, in short “Radionuclide Calibrators” and “Contaminometers for alpha, beta, gamma radiations “

(ii) Renewal of the Authorizations for Radiological Security for all kinds of Standard Sources and Solutions which are produced and distributed to purchasers.

4.2. IMPLEMENTATION OF THE QUALITY MANAGEMENT IN MEASUREMENT

The referential is the SR EN ISO/IEC 17025:2005 “General requirements for the competence of testing and calibration laboratories”

Several types of recognition of the Quality System of the Radionuclide Metrology Laboratory (RML) are required.

(i) On the international scale, one mentions the Recognition, by the Technical Committee-Quality, EUROMET, that IFIN-HH, as a designed member of the Technical Committee-Ionizing Radiations (TC-IR) of EUROMET, fully implemented the Quality System (QS) in the whole Ionizing Radiations Laboratory, including RML.

(ii) At the national level, several recognitions of the QS were obtained up to now, such as:

- The Laboratory was evaluated and attested by the Romanian Bureau of Legal Metrology as a calibration laboratory for activity measurements, Attestation no. B-12-20-05/2005
- The CNCAN designed our laboratory as a Notified Standardization/ Calibration Laboratory for the Nuclear Field, Notification LE 02/2005, according to the SR EN ISO/IEC 17025.

(iii) The new step in recognition of the quality system is the accreditation by the RENAR, both for standardization/calibration and for low level radioactivity measurement. A detailed presentation of the system is made in the paper [9]. The whole quality documentation was submitted to the RENAR, and several audits were carried out: Two internal, IFIN-HH audits and a Management Review meeting were organized at the IFIN-HH level. A pre-assessment evaluation of the LMR was made by Michael J Woods, from the Ionising Radiations Metrology Consultants (IRMC), UK, an internationally recognized expert in the field, during

April 2006; M. J. Woods elaborated a consistent, positive report, which was considered by the LMR in reviewing the documentation and which was attached to the accreditation application.

(iv) The specific aspects of the QS in the QA for nuclear medicine measurements.

These requirements regard some Technical Procedures which were specially elaborated:

- Metrological checking of the Radioisotope Calibrators, code AC-PL-LMR-11.

Such as it was shown, this equipment is under the metrological control of the state, according to the metrology law. To obey these requirements, the official procedure, codified as P39-99, of the BRML- INM (National Institute of Metrology), for testing and metrological check, was taken as reference document. The procedure AC-PL-LMR-11 is now applied in all the metrological checks of radioisotope calibrators belonging to the hospitals, that our laboratory currently carries out. A new problem occurred during the metrological check of calibrators. Some old equipment still maintained the technical conditions, but were de-calibrated during the utilization. If we automatically rejected them after the check, their owners could not measure radiopharmaceuticals until new calibrators were purchased, in many cases a very difficult task. In these circumstances we decided to write a technical instruction for their recalibration, AC-IL-LMR-12, where the conditions of acceptance and calibration procedures, by the use of standard solutions prepared in RML, are well established.

- Calibration of the Equipment used in the Physico-chemical Analyses Laboratory of the Radioisotope Department, code AC-PL-LMR-12.

This procedure was necessary as we are required to calibrate special equipment for analyses of radiopharmaceuticals, whose production is under GMP rules approval; the analyses laboratory is under RENAR accreditation. In both cases, the equipment calibration certificates are compulsory documents. The equipment periodically calibrated are: The Radiochromatograph for the control of Radiochemical Purity, and the Gamma counter for Radio Immuno Analyse.

- Organisation of interlaboratory comparisons regarding the measurement of activity of the radioactive sources and solutions, code AC-PL-LMR-07.

In writing this procedure, the previous experience in organisation of national comparisons, mainly for radiopharmaceuticals [10, 11], as well as the specific applicable standards such as: ISO Guide 43 “Proficiency testing by interlaboratory comparisons” Part 1: “Development and operation of proficiency testing schemes” and Part 2: “Selection and use of proficiency testing schemes by laboratory accreditation bodies”, were taken into account. Within the frame of the IAEA CRP E.2.10.05, a new national comparison, regarding the measurement of ^{131}I solution in hospitals, under supervision of CNCAN, is on way.

CONCLUSIONS

The Radionuclide Metrology Laboratory, as a primary radioactivity standard, is fully implied in the accomplishment of the practical measurement requirements for nuclear medicine.

The participation in international, CIPM and IAEA, projects allowed the demonstration of its capability to cover the entire traceability chain from the international level to the end users, hospitals.

The newest upgrading of the RML equipment and implementation of quality system is the warranty for quality assurance in Romanian nuclear medicine measurement field.

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