National and International Comparisons on Radiopharmaceuticals’ Activity Measurement

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The paper presents the experience gained by the Radionuclide Metrology Laboratory (RML) from IFIN-HH in the assurance of the whole traceability chain within the last period: Absolute standardization of radionuclides used in the preparation of radiopharmaceuticals to be used in Nuclear Medicine and participation at international comparisons; Assurance of the international traceability in the field of radioactivity measurement, recognized by the approval of 34 Calibration and Measurement Capability (CMC) files, and publication on the CIPM-MRA Annex C Data Base, www.bipm.org, in 2008; Organization of national comparisons with interested units, as the subsequent link of traceability chain. Particularly, the paper focuses on the methods for standardization of Co-57, Tc-99m, as well as on the participation of RML at the international comparison regarding the measurement of Tc-99m mock radionuclide Co-57, and organization of a national Tc-99m comparison in 2008, as a part of the research work within the frame of the IAEA’s CRP E2.10.05.

Key words: Radiopharmaceuticals measurement, Co-57, Tc-99m, international and national comparisons, JCRB – approved CMCs.

1. INTRODUCTION

The Radionuclide Metrology Laboratory (RML) from IFIN-HH has a long experience in the assurance of the traceability in radioactivity measurements, from the international level to the end users, by developing methods for primary standardization of radionuclides, participation at international comparisons and by implementing the Quality System, approved by the Technical Committee – Quality (TC-Q) of EURAMET. These achievements were internationally recognized by the approval of 34 Calibration and Measurement Capability (CMC) files, in the field of radioactivity measurement, by the Joint Committee of the Regional Organizations and


BIPM (JCRB), and their publication on the CIPM-MRA, Annex C-Data Base, in 2008. These general aspects were presented in the papers [1–3]. On the other side, there is a growing international interest of the primary national standard laboratories for the control of radioactivity measurements performed in their countries, mainly in the field of radiopharmaceuticals, in production units and in nuclear medicine clinics [4, 5]. These measurements are performed by using commercial radionuclide calibrators, provided with reentrant ionization chambers. Regarding the Romanian metrology legislation, the calibrators are included in the official list of measurement means under the control of the state. The International Atomic Energy Agency (IAEA) conducted a Coordinated Research Project (CRP) E2.10.05 “Harmonization of quality practices for nuclear medicine radioactivity measurements”. Among the results of this CRP, one mentions: Elaboration of the document TRS 454 [6], of the protocols for participation of the national laboratories at international comparisons and for organization of the national comparisons with nuclear medicine units [7]. RML participated at the IAEA comparison, 2006 [8] and organized, in 2007, a national comparison for the radionuclide I-131 [9]. A very important radionuclide for nuclear medicine is Tc-99m, used in most diagnostic clinics. Due to its short half life, it is very difficult to organize an international comparison. The participants at the CRP E2.10.05 decided that a Co-57 comparison must be organized by IAEA, in 2008, as this radionuclide has similarities with Tc-99m concerning the energy and intensity of emitted gamma radiations and may be considered a satisfactory mock for Tc-99m; RML took part in this comparison, whose results are under final evaluation. However, our laboratory had organized previously a national Co-57 comparison, reported in paper [1]. Regarding the radionuclide Tc-99m, it was decided to organize genuine Tc-99m national comparisons by the CRP participant laboratories. For this radionuclide, our previous work referred at a limited comparison within in the Radioisotope Department (RD) [1]. The most recent work, reported in this paper, focused on the primary standardization of solutions and organization of a national comparison with the RD of IFIN-HH and Romanian nuclear medicine clinics.

2. PREPARATION AND STANDARDIZATION OF SOLUTIONS

In the case of the radionuclide $^{57}$Co, the solution was prepared in RML by using an imported radiochemical product; for the IAEA comparison, a solution prepared and distributed by the QSA Global GmbH-Germany was received. $^{57}$Co is a radionuclide decaying by electron capture process; the standardization was done by using the $4\pi$PC-$\gamma$ coincidence method, efficiency extrapolation variant [10]. For
the 2008 comparison, a new absolute standardization was performed and a new value of the calibration factor of the secondary standard, CENTRONIC IG12/20A ionization chamber, with an improved uncertainty, was determined [11]. The measurement result was sent to the IAEA. According to the organizer’s reports, RML obtained a satisfactory result, such as it is presented in the papers [12, 13]. In the case of the radionuclide Tc-99m, several solutions were prepared, either by elution from commercial generators, or by extraction in RD from Mo-99 solution. Tc-99m is a radionuclide difficult to be absolutely standardized, as it decays by isomer transition. First calibration of the CENTRONIC IG12/20A ionization chamber had been based on the use of Tc-99m sources prepared from solution and relatively standardized by the gamma-ray spectrometry method, using a HPGe detector calibration curve. More recently, RML elaborated an original absolute method of standardization, based on the coincidence method [14]. A new calibration of the ionization chamber was thus performed, the agreement between the two calibration factor values being very satisfactory [11]. RLM developed a Quality System (QS), as a Calibration Laboratory in the field of Radioactivity, according to EN ISO/IEC 17025:2005. The QS includes the Quality Manual and the whole set of System and Work Procedures (WP) and Instructions. Both calibrations were performed by following the RML-WP, AC-PL-LMR-02, “Calibration of the RML equipment for relative standardization” and Work Instruction AC-IL-LMR-02-02, “Calibration of the installation with ionization chamber in 4πsr geometry and electrometer”.

3. ORGANIZATION OF THE TC-99M COMPARISON


3.1. PREPARATIVE STEPS

The conception of comparison was adapted to the measurement conditions of a short life radionuclide; it was not possible to send vials with standard solution to
the participants, due to the short half life of $^{99m}\text{Tc}$, $T_{1/2}=6.0067$ h, and due to the exclusive use of imported ($^{99}\text{Mo}+^{99m}\text{Tc}$) generators in Romanian hospitals. The RML contacted the interested units and all agreed with the following procedure: The units elute the Tc-99m from their generators, measure the vial containing it, according to their routine procedures, fill-in the Comparison Form, AC-PL-LMR-07-03, and send them to RML, in order to be re-measured. Alternatively, a single vial is measured by several participants. In the case of RD, the vial received from a hospital was measured. In some cases, such as for the Radioisotope Production Department of IFIN-HH, the participation in both I-131 and Tc-99m comparisons was a part of the RENAR Accreditiation process of the Analyses Laboratory (CPRLAB – 2008 accredited laboratory).

3.2. COMPARISON

Each participant eluted his own generator in a 5 mL vial, type P6 or equivalent, identical to the vial used in the normal work. Table 1 presents the participant units and the responsible persons.

<table>
<thead>
<tr>
<th>No.</th>
<th>Laboratory</th>
<th>Responsible person</th>
<th>Sample code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RD-IFIN-HH</td>
<td>Dr. Catalina Cimpeanu</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>RD-IFIN-HH</td>
<td>Chim. Catalina Barna</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>RD-IFIN-HH</td>
<td>Dr. Catalina Cimpeanu</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Spitalul Militar Central „Dr. Al. Davilla” Bucuresti</td>
<td>Dr. Paul Cornel Murgoci</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Spitalul „Sf. Ioan” Bucuresti</td>
<td>Dr. Mirela Gheorghe</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Institutul „C.I. Parhon” Bucuresti</td>
<td>Dr. Florin Alexiu</td>
<td>3</td>
</tr>
</tbody>
</table>

They measured the activity using their radionuclide calibrators and reported the technical data required by the form AC-PL-LMR-07-03. The activity value, $A_R$, expressed in MBq, or mCi in the case of old calibrators, and its uncertainty, $u_c\%$, for a coverage factor $k = 1$, was reported for the hospital measurement time. Other technical data refer to the following aspects: equipment type, calibration/metrological verification status, other checks. All the participants used the 5 mL, Tc-99m, vial calibration factors, determined by the calibrator producers or by the RML. Supplementary checks in hospitals refered at: measurement of background values, indication of check sources: Co-57, Ba-133, Co-60, Cs-137, decay corrections. Table 2 presents the reported data.
As it results from the Table 2, some laboratories used the calibration factors provided by the equipment producers. RLM carried out calibration for 4 instruments. The metrological check is carried out at intervals longer than one year, although the Metrology law and Technical Metrology Instruction IML3–04 require annual check.

The vials were then transported to RML-IFIN-HH. The activity was measured in RML, by using the secondary standard CENTRONIC IG12/20A calibration factor for a 5 mL, Tc-99m, vial; its value depends on the volume of solution and type of vial. The activity value determined at RML is the Conventionally true, or Reference value, $A_{CA}$, with its uncertainty, $u_{c/1}$ %, calculated for a coverage factor $k = 1$, at the reference time.

### 3.3. PROCESSING OF DATA AND COMPARISON RESULT

All reported data were processed at RML: (i) Decay correction of reported data for the reference time; (ii) Calculation of the relevant parameters: $R = A_R/A_{CA}$, ratio of reported and conventionally true activity; the difference, $U = (R - A_{CA}) / A_{CA}$, %; the deviation normalized with respect to the stated uncertainty (according to EAL-P7 publication)

$$E_n = U / (k \sqrt{u_1^2 + u_2^2})$$

$k = 2$, for those participants who reported measurement uncertainty. The result was declared as acceptable for those results having obtained $E_n < 1$. Table 3 summarizes the comparison result.
### Table 3
Comparison result

<table>
<thead>
<tr>
<th>Participant</th>
<th>Calibrator</th>
<th>Reference time</th>
<th>(A_{CA}, \text{MBq} )</th>
<th>(u_1, %)</th>
<th>(A_R, \text{MBq})</th>
<th>(u_2, %)</th>
<th>(R)</th>
<th>(U,%)</th>
<th>(E_n)</th>
<th>(E_{nl} &lt; 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1a</td>
<td>Capintec CRC-15R</td>
<td>05.06.2008 12:00 h</td>
<td>785.9±11.8 (1.5 %)</td>
<td>2.5</td>
<td>805.7</td>
<td>2.5</td>
<td>1.02</td>
<td>5</td>
<td>2.5</td>
<td>0.43</td>
</tr>
<tr>
<td>L1b</td>
<td>Picker</td>
<td>05.06.2008 12:00 h</td>
<td>785.9±11.8 (1.5 %)</td>
<td>4.0</td>
<td>832.3</td>
<td>4.0</td>
<td>1.05</td>
<td>9</td>
<td>5.9</td>
<td>0.69</td>
</tr>
<tr>
<td>L1c</td>
<td>Capintec CRC-15R</td>
<td>05.06.2008 12:00 h</td>
<td>785.9±11.8 (1.5 %)</td>
<td>1.2</td>
<td>790.0</td>
<td>1.2</td>
<td>1.00</td>
<td>5</td>
<td>0.5</td>
<td>0.13</td>
</tr>
<tr>
<td>L2a</td>
<td>Curiementor 2</td>
<td>05.06.2008 12:00 h</td>
<td>785.9±11.8 (1.5 %)</td>
<td>3.0</td>
<td>782.7</td>
<td>3.0</td>
<td>0.99</td>
<td>6</td>
<td>–0.4</td>
<td>0.06</td>
</tr>
<tr>
<td>L2b</td>
<td>Curiementor 3</td>
<td>05.06.2008 12:00 h</td>
<td>785.9±11.8 (1.5 %)</td>
<td>0.7</td>
<td>749.5</td>
<td>0.7</td>
<td>0.95</td>
<td>4</td>
<td>–4.6</td>
<td>1.39</td>
</tr>
<tr>
<td>L3</td>
<td>Picker</td>
<td>13.12.2007 12:00 h</td>
<td>324.8±4.9 (1.5 %)</td>
<td>6.0</td>
<td>349.9</td>
<td>6.0</td>
<td>1.07</td>
<td>7</td>
<td>7.7</td>
<td>0.62</td>
</tr>
<tr>
<td>L4</td>
<td>Curiementor 3</td>
<td>19.03.2009 8:25 h</td>
<td>1685±25 (1.5 %)</td>
<td>1.0</td>
<td>1634</td>
<td>1.0</td>
<td>0.97</td>
<td>0</td>
<td>–3.0</td>
<td>0.83</td>
</tr>
</tbody>
</table>

3.4. CONCLUSIONS OF THE COMPARISON

1. From a total number of 7 reported values, a number of 5 results are within < 5% difference from the reference value, and 7 results within the limit < 10%, a proportion of 100% from participating units, being in compliance with the European Pharmacopoeia and Metrology Norm NTM 3–99 requirement for the assurance of a maximum 10% uncertainty in radiopharmaceuticals activity measurement in hospitals.

2. The mean value of the ratio \(R = A_R/A_{CA}\), by considering all the 7 reported values is \(R = 1.012 (S_{n-1} = 4.9\%)\). The results are approximately normally distributed, 71% of the results being situated at a 1σ (\(S_{n-1}\)) difference level, and 100% results at a 2σ difference.

3. For those participants who reported uncertainties, the acceptance criterion EAL-P7, 1996 was applied. As it can be seen from the Table, the participant L2b underevaluated the uncertainty; although its difference from the reference value is smaller than 5% and also smaller than L3, the \(E_n\) criterium eliminates it and accepts the participant L3, having a higher difference, 7.7%, but a more realistic uncertainty evaluation.

4. GENERAL CONCLUSIONS

- RML is internationally recognized due to good results obtained in more than 30 International Comparisons of Radioactive Standard sources and solutions.
Absolute standardization and new calibrations of the secondary standard, CENTRONIC IG12/20A, were performed for Co-57 and Tc-99m.

- The absolute standardization of Tc-99m is original.
- RML, IFIN-HH participated at the Co-57 comparison, organized by IAEA.
- RML organized a Tc-99m national comparison with 7 radionuclide calibrators, belonging to 4 units. All the calibrators had a deviation lower than 10% and 5 of them lower than 5% from the RML reference value.
- The calibrators being calibrated/checked by RML passed the test.

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REFERENCES


