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Review

Traceability for nuclear medicine: the status of primary radioactivity standards

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Abstract

The medical use of radionuclides depends on the accurate measurement of activity (Bq) for regulatory compliance, patient safety, and effective treatment or image quality. In turn, these measurements rely on the realization of primary standards of activity by national metrology institutes, with uncertainties that are fit for purpose. This article reviews the current status of primary standards of activity for radionuclides used in medical imaging and therapy applications. Results from international key comparisons carried out through the International Bureau of Weights and Measures transfer instruments (SIR and SIRTI) are used to verify that standards for a variety of radionuclides are consistent and conform with practitioners' expectations.

Keywords: traceability, nuclear medicine, radioactivity standard, key comparison, targeted therapy

(Some figures may appear in colour only in the online journal)

1. Introduction

The accurate measurement of the radioactivity content of pharmaceuticals used in diagnostic imaging and for radiopharmaceutical therapy is essential to ensure patient safety, to yield diagnostically useful medical images and to effectively treat disease. This importance is reflected in pharmaceutical regulations, drug licenses, and requirements for clinical trials [1]: radiopharmaceutical products typically cannot enter human trials or be marketed unless the radioactivity content (Bq) of the drug has been measured in a way that is traceable to national or international standards.

An earlier article [2] summarized how the traceability chain is established for clinics and manufacturers of radiopharmaceuticals. This article is a review of the status of the first step in this chain, posing the question: 'Are the primary radioactivity standards for applications in nuclear medicine deemed fit for purpose by the clinicians and researchers who use them?' Answering this question requires comparing the primary standards of different countries, a *raison d'être* of the international measurement system.

The system for ensuring global comparability of measurements was established in 1875 when the Meter Convention was signed. This treaty established the International Bureau of Weights and Measures (BIPMs), an international organization through which governments act together on matters related to measurement science. The BIPM is under the authority of

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the General Conference on Weights and Measures (CGPMs), which elects the International Committee for Weights and Measures (CIPMs); this committee has 18 members and its role is to oversee the operation of the international measurement system. The CIPM is advised by technical committees (Consultative Committees) which cover specific fields of metrology—the committee for ionizing radiation metrology is the Consultative Committee for Ionizing Radiation (CCRI).

The system was enhanced at a meeting of the CGPM in 1999 by the adoption of the CIPM Mutual Recognition Arrangement (CIPM MRA) [3]. This arrangement sets the framework through which national metrology institutes (NMIs) demonstrate the international equivalence of their measurement standards and the calibration and measurement certificates they issue. Many of the laboratories providing the national measurement standards in ionizing radiation are designated institutes (DIs); in this paper, the term 'NMI' is meant to include these DIs.

One requirement of the CIPM MRA is that metrology institutes compare their standards to those of other countries. The results from comparison exercises are published in the key comparison database (KCDB) [4]; this body of data gives users the opportunity to review the status of primary standards of radioactivity for applications in medicine and assess the work needed to ensure these standards conform with the need and are useful.

The article is divided in three parts. The first part describes how international comparisons of radioactivity standards are conducted. Second, an overview of the important radionuclides for nuclear medicine (Single Photon Emission Computed Tomography (SPECT), positron emission tomography (PET), therapy/theragnostic, *in-vitro* diagnosis) is presented with their status in terms of measurement maturity. Finally, the results from international comparisons of standards are evaluated to assess how well primary standards conform to the expectations of different stakeholders (tolerance limits from 1% to 5%).

2. International comparisons

Over the years, NMIs have developed many different techniques for realizing primary standards of radioactivity; an overview has been published in a special issue of *Metrologia* [5]. The many techniques constitute a particular strength of the field, as these techniques have different technical challenges, and consistent results can help demonstrate that the primary standard is robust.

Three general approaches to compare primary standards have been adopted by NMIs. The first technique is for one institute (the 'pilot' institute) to produce a set of ampoules from a master solution and distribute them to other participants. Each institute determines the activity (generally per g) of the radionuclide using one or more primary standardization techniques, and the results are compared to a consensus value [the so-called key comparison reference value (KCRV)]. The convention in radionuclide metrology is to use a power-moderated weighted mean [6] to define the KCRV, as the method gives a systematic way to deal with data sets with different degrees of inconsistency and is robust against discrepant results.

The difference D between a measured value and the KCRV, along with the associated uncertainty U at a 95% level of confidence, is expressed as a pair of terms (D, U) called the degree of equivalence (DoE). The DoE is taken to mean the degree to which the standards are consistent with the KCRV and hence are consistent with each other. Signatories of the CIPM MRA [3] agree to recognize the DoEs of participating metrology institutes and the validity of calibration and measurement certificates.

The DoE (D_i, U_i) for the ith participant is given by

$$\begin{aligned} D_i &= \text{difference, } A_i - \text{KCRV, between the measured value } (A_i) \text{ and the KCRV,} \\ U_i &= 2u(D_i), \text{assuming underlying normality,} \end{aligned}$$

with

$$u^2(D_i) = u_i^2 - u^2(\text{KCRV}). \tag{1}$$

The CCRI has adopted the definition below for the variance in the result (taken from Ratel [7]).

$$u^2(D_i) = (1 - 2w_i)\,u_i^2 + u^2(\text{KCRV}), \tag{2}$$

where w_i is the weight of the contribution of laboratory i's result in the calculation of the KCRV and u_i is its corresponding standard uncertainty.

This type of comparison exercise has the advantage that many NMIs can compare standards for a particular radionuclide in one exercise over a relatively short timescale. The disadvantages are that the exercise can be costly and complex for the pilot institute, and exercises can take place only infrequently. To avoid these problems, the international radionuclide metrology community has adopted a second approach, using a set of high-precision, highly stable, transfer instruments housed in the Ionizing Radiation Department facilities at the BIPM. A sample of a standardized solution of the radionuclide is measured on one of the transfer instruments and compared to the aggregated response of the instrument to standards from participating NMIs. The KCRV and DoE are calculated in a similar way as above.

To date, three instruments (the SIR, the SIRTI and the ESIR) have been developed for comparing standards of gamma-ray-emitting radionuclides and pure alpha- and beta-particle-emitting radionuclides, respectively. The ESIR was launched recently (2020), so results from this instrument have yet to be published, but a pilot study measuring ^{60}Co standards is ongoing to test the ESIR against the SIR [7–9].

The so-called International Reference System (*Système International de Référence*—SIR) was established in 1976 as a precise method to compare national standards of gamma-ray-emitting radionuclides [10]. The instrument chosen for the SIR, a re-entrant ionization chamber (figure 1), has a track record for long-term stability. An NMI dispenses a sample of a standardized solution in a glass ampoule and then the ampoule, along with the institute's estimate of the activity and its uncertainty, is dispatched to the BIPM.

Figure 1. The ionization chambers used for the international reference system for gamma-emitting radionuclides (the SIR) at the BIPM. The photograph was taken during construction of the instrument with the lead shield partially completed and it shows two re-entrant ionization chambers (the second chamber is a back-up in case of problems with the main instrument). NMIs send a sample of the radionuclide in solution in a glass ampoule; the ampoule is placed in a holder and lowered into the well in the chamber (the hole can be seen at the top of the chambers). The current produced in the chamber is proportional to the activity of the radionuclide in the sample.

Figure 2. The international reference system for short-lived gamma-emitting radionuclides (SIRTI). The instrument comprises a NaI(Tl) detector in a lead shield, mounted on a tripod. Samples for measurement are placed in a well in the detector (not visible in the photograph).

The ampoule is placed in the ionization chamber and the current, I_s, produced is measured; the sample is then replaced by a sealed radium source j that produces a current, I^j_{Ra}, close to that produced by the sample. The radium source is chosen from a set of five sources $j = (1,\ldots,5)$ of different activities. The result is expressed as the quotient of the current produced by the sample and the radium source. This approach reduces the uncertainty due to any non-linearity of the electrical current measurement system and measurements will not depend on the calibration of the capacitors. An equivalent activity, $A_{e,i}$ is defined as 'the activity that would produce a current equal to the current produced by the radium source of the highest activity':

$$A_{e,i} = A_{s,i}\frac{I^j_{Ra}F_j}{I_{s,i}}, \tag{3}$$

where $A_{s,i}$ = activity of the source as determined by NMI i,

I^j_{Ra} = current produced by radium source number j,

$I_{s,i}$ = current produced by the source provided by NMI i,

$F_j = \frac{I^5_{Ra}}{I^j_{Ra}}$ = normalizing coefficient,

which is the quotient of the current produced by the most active radium source ($j = 5$) to radium source j based on multiple measurements of the radium sources.

Corrections are made for radioactive decay, impurities and background current, which for simplicity have been omitted from the above equations.

The KCRV for this type of comparison exercise shows the results in terms of an 'equivalent activity'. The convention adopted for the SIR is that all measurements of a given primary standard from a given NMI since its initial measurement on the instrument contribute to the calculation of the appropriate KCRV. One advantage of this approach is that primary standards in use today can also be compared to those realized many years ago, when time-stamped, demonstrating the degree of consistency of dispensed activity since the original clinical trials of the radiopharmaceutical.

The SIR enables NMIs to compare their primary standards at any time, with the need to ship only a single radioactive source. However, many radionuclides used in nuclear medicine have very short half-lives (on the order of hours or minutes) and cannot be measured on the SIR as they decay too much during shipment. A third approach, therefore, was to develop a stable, reproducible and robust instrument that could be used on-site at the NMI rather than rely on submission of a source to the BIPM. This SIRTI (SIR Travelling Instrument), first used in 2013 [11], consists of a 75 mm × 75 mm NaI(Tl) crystal with a well at the center for the source, mounted on a tripod and shielded from background radiation using a lead shield (figure 2). Measurements are based on the number of pulses per second with a height above a fixed reproducible threshold from the ^{93m}Nb x-ray peak [11].

In summary, three methods have been used to date for international comparisons of primary standards of radioactivity: one-off exercises led by a pilot institute, on-going comparisons of sources submitted to the BIPM (the SIR) and on-going comparisons using the SIRTI at individual institutions. One feature of radionuclide metrology is that the results from these exercises can be combined: if an institute has participated in a one-off exercise and has submitted a sample to the SIR, the results from the exercise can be linked to all the results from the SIR measurements, leading to an update of the DoEs for the radionuclide and, rarely, resulting in a revised KCRV. The details of the calculations are given in the reports published in the KCDB [4].

3. The measurement methods matrix (MMM)

Given the limited resources available at NMIs, it is not feasible to conduct comparison exercises for every radionuclide. The CCRI agreed in 2003 that successful participation in a comparison exercise for one radionuclide could be acceptable as evidence that the NMI could realize primary standards of other radionuclides with a similar decay scheme using the same standardization technique. Radionuclides are listed in the stub (first) column and primary measurement techniques are laid out across the header (first) row of an extensive table, which is called the MMM. The MMM, available to metrology institutes on the BIPM website, continues to be updated as results from comparisons and technical activities add new radionuclides or methods are improved. Applying the MMM can be complex, as the system must account for the decay scheme, the method used and the degree of difficulty [difficult (red), moderately difficult (yellow) or relatively easy (green)] of applying the particular method to a radionuclide with a decay scheme of that type. The degree of difficulty is assessed by the CCRI. It is therefore not possible to state that a comparison of primary standards of one radionuclide is necessarily direct evidence for all other radionuclides in the same 'family' (i.e. measured by the same primary method), but the MMM does provide important support for optimizing comparisons in radionuclide metrology. Further details of this system are given under guidance documents at the CCRI Section II home page [12]and by Karam *et al* [13].

The MMM has been used to support claims by NMIs for calibration and measurement capabilities (CMCs) as set out in the CIPM MRA. A CMC is a quantitative description of a service offered by the institute; all claims are peer-reviewed before publication on the KCDB. It permits the laboratory to demonstrate its traceability to the international system of unit (SI) in conformance with the requirements of ISO/IEC 17025 [11]. The review includes a critical assessment of traceability of the service to a primary standard that has been shown to be equivalent to primary standards from other institutes. The MMM is a key link between a primary standard and an international comparison of standards of another radionuclide.

An investigation of the published CMCs by one or more metrology laboratories (and summarized in this review) show potential gaps where no primary standards exist. Since publication of a CMC is not compulsory, it is possible that primary standards have been realized for some radionuclides but are not listed. If no primary standard has been realized, measurements rely on other techniques such as high-resolution gamma-ray spectrometry and published decay data and will usually be subject to additional standard measurement uncertainties of a few percent; traceability to primary standards would be through the calibration of the spectrometer.

4. Radiopharmaceuticals

There are more than 40 million nuclear medicine procedures performed per year worldwide [14], of which 90% are for diagnostics with the remainder for radiopharmaceutical therapy. The most-used radionuclide is ^{99m}Tc, which accounts for 85% of diagnostic imaging for managing patients with renal, hepatic, hepatobiliary, bone, cardiac and oncological diseases [15]. The key advantages of this radionuclide are that it is easy to produce in the nuclear medicine clinic from a transportable ^{99}Mo/^{99m}Tc generator and there is a wide range of compounds that can be labeled for different imaging applications (a summary has been published in an OECD/NEA report [16]).

Many different radionuclides are used for a range of applications in therapy and diagnosis. Using single photon emission computed tomography (SPECT), for example a 3D image of the distribution of the radionuclide in the patient's body can be obtained. Radionuclides used for this technique emit one or more gamma rays at an energy that can be detected easily outside the body (around (100–300) keV). The half-life of the radionuclide being used for the procedure must be sufficiently long that the radiopharmaceutical can be shipped to the clinic with the appropriate level of activity at the time it is used, or must be available from a generator, such as ^{99}Mo/^{99m}Tc. PET reconstructs images from positron annihilation radiation; radionuclides for this imaging technique have very short half-lives (some on the order of minutes) and are produced by local (often on-site) cyclotrons.

For radiopharmaceutical therapies, the half life of the radionuclide is generally longer and emissions with high linear energy transfer are preferred so that the radiation dose is delivered preferentially to the target (e.g. the tumor) while sparing nearby healthy tissue. Alpha and beta-particle emitting radionuclides are used, but there is also interest in using low-energy Auger electron-emitting radionuclides such as those that decay by electron-capture [17, 18].

Finally, radionuclides are also used for *in-vitro* diagnostic assays, such as for the detection of pathogens or specific metabolites [19]. The chemical properties of the element for labeling purposes are more important than the radiological properties, so a range of radionuclides with relatively long half-lives (e.g. ^{125}I, ^{3}H) are generally used.

The radionuclides used for different applications have different characteristics depending on technical requirements and physiological targets, so in assessing the status of primary standards it can be useful to group them by application. Tables 1–4 list the radionuclides currently in use or being studied for potential future products, including the radionuclides identified by the World Nuclear Association [14], European PRISMAP network [20] (a consortium of research centers active in the development of radiopharmaceuticals), the US Department of Energy Isotope Program (DOE IP) [21], supporting the development and distribution of radionuclides for cancer therapy, diagnostic imaging, and nuclear science research.

The metrological status of each radionuclide is also provided, based on:

- The number of results from primary measurements used in the calculation of the KCRV of BIPM(II).K1 comparison (as they never lapse, an accurate DoE can be obtained when sending an ampoule to the SIR, whatever the existing number of current DoEs),

Table 1. Radionuclides used for single photon emission computerized tomography (SPECT).

Radionuclide	Example uses	Participations in BIPM services	Number of current DoEs	Number of CMCs
^{47}Sc	Theranostic (beta therapy + SPECT) [14, 20]	0[a]	0	4
^{67}Cu	Theranostic (beta therapy + SPECT) [14, 20]	0	0	0
^{67}Ga	Cancer imaging [14]	8	5	27
^{99}Mo	Parent radionuclide for ^{99m}Tc [14, 21]	3	0	10
^{99m}Tc	Skeleton/cardiac imaging [14, 21]	4	16	32
^{111}Ag	Theranostic (beta therapy + SPECT) [20]	1	0[b]	0
^{111}In	Infection/inflammation imaging [14]	7	2	20
^{123}I	Diagnostic thyroid disease [14]	4	0[c]	17
^{133}Xe	Imaging lung function [14]	4	0	11
^{135}La	Theranostic (targeted Auger therapy + SPECT) [14]	0	0	0
^{153}Sm	Theranostic (beta therapy + SPECT) for bone cancers [14, 20]	4	4[d]	13
^{155}Tb	Part of the terbium quadruplet for Theranostic [20, 22]	0	0	0
^{161}Tb	Theranostic (beta therapy + SPECT) [20]	1	0	0
^{167}Tm	Theranostic (beta therapy + SPECT) [23]	0	0	0
^{166}Dy	Parent nuclide for ^{166}Ho [24]	0	0	0
^{166}Ho	Theranostic against liver metastases [25]	1	0[e]	0
^{169}Yb	Cerebrospinal fluid studies in the brain [14]	6	0	26
^{177}Lu	Theranostic (beta therapy + SPECT) [14, 21]	5	11	7
^{186}Re	Theranostic (beta therapy + SPECT)/pain relief in bone cancer [14]	1	1	4
^{195m}Pt	Preclinical imaging and screening [26]	0	0	0
^{201}Tl	Diagnostic heart disease [14]	6	4	24
^{213}Bi	Theranostic (targeted alpha therapy + SPECT) [14, 20, 21]	0	0	0

[a] Only one ampoule from JRC has been measured by the SIR in 1983, so no KCRV was calculated.
[b] One result from NPL measured by the SIR in 2011.
[c] The SIRTI comparison BIPM.RI(II)-K4.I-123 will soon be opened.
[d] The SIRTI comparison BIPM.RI(II)-K4.Sm-153 will soon be opened.
[e] One submission from CMI. A EURAMET.RI(II)-K2 comparison is planned.

Table 2. Radionuclides used for positron emission tomography (PET).

Radionuclide	Example uses	Participations in BIPM services	Number of current DoEs	Number of CMCs
^{11}C	Diagnostic of prostate cancer [14] and brain imaging in Alzheimer disease	1	0[a]	3
^{13}N	Myocardial perfusion imaging [14]	0	0	0
^{15}O	Quantifying blood flow [14]	0	0	0
^{18}F	Hodgkin's disease, non-Hodgkin lymphoma, colorectal cancer, breast cancer, melanoma, lung cancer and Alzheimer's disease [14]	5	14	18
^{44}Sc	Alternative to ^{68}Ga [20]	0	0	0
^{44}Ti	Parent radionuclide for ^{44}Sc [27]	0	0	0
^{64}Cu	Diagnostic of prostate cancer [14, 20]	4	7	5
^{68}Ga	Neuroendocrine tumors [14]	0	0	2
^{68}Ge	Parent radionuclide for ^{68}Ga [14]	4	17	8
^{82}Rb	Diagnostic heart disease [14]	0	0	0
^{82}Sr	Parent radionuclide for ^{82}Rb [14]	0	0	0
^{89}Zr	Immuno-PET imaging [28]	0	0	0
^{124}I	Diagnostic of thyroid cancer [14]	0	0	2
^{149}Tb	Diagnostic of prostate cancer [20]	0	0	0
^{152}Tb	3 photons imaging [20]	0	0	0

[a] Comparison with the SIRTI is in progress BIPM.RI(II)-K4.C-11.

Table 3. Radionuclides used for therapy.

Radionuclide	Example uses	Participations in BIPM services	Number of current DoEs	Number of CMCs
^{32}P	Beta therapy for blood disorders [14]	0	0[a]	25
^{47}Sc	Theranostic (beta therapy + SPECT) [14, 20]	0	3	4
^{60}Co	Brachytherapy [14, 21]	27	18	40
^{67}Cu	Theranostic (beta therapy + SPECT) [14, 20]	0	0	0
^{89}Sr	Beta therapy for metastatic prostate cancers [14, 21]	0	0[b]	24
^{90}Sr	Beta therapy for conjunctival melanoma [14, 21]	0	0[c]	3
^{90}Y	Radioembolization beta therapy [14]	1	8[d]	14
^{103}Pd	Brachytherapy [14]	0	0	0
^{111}Ag	Theranostic (beta therapy + SPECT) [20]	1	0[e]	0
^{125}I	Brachytherapy [29]	0	22	36
^{131}I	Beta therapy against thyroid cancer [14]	15	17	52
^{131}Cs	Brachytherapy against prostate cancers [14]	0	0	1
^{135}La	Theranostic (targeted Auger therapy + SPECT) [14]	0	0	0
^{153}Sm	Theranostic (beta therapy + SPECT) for bone cancers [14, 20]	4	4[f]	13
^{161}Tb	Theranostic (beta therapy + SPECT) [20]	1	0	0
^{167}Tm	Theranostic (beta therapy + SPECT) [23]	0	0	0
^{165}Dy	Radiosynovectomy against articular pain [14]	0	0	1
^{166}Dy	Parent nuclide for ^{166}Ho [24]	0	0	0
^{166}Ho	Theranostic for liver metastases [25]	1	0[g]	0
^{165}Er	Targeted Auger therapy [20]	0	0[h]	0
^{169}Er	Targeted beta therapy for metastasized cancers [14, 20]	0	0	1
^{165}Tm	Parent nuclide for Er-165 [30]	0	0	0
^{175}Yb	Targeted beta therapy [20]	0	0	0
^{177}Lu	Theranostic (beta therapy + SPECT) [14, 21]	5	11	7
^{188}W	Parent nuclide for Re-188 [21, 31]	0	0	0
^{186}Re	Theranostic (beta therapy + SPECT)/pain relief in bone cancer [14]	1	1	4
^{188}Re	Targeted beta therapy [14, 32]	0	0	7
^{212}Pb	Parent nuclide for ^{212}Bi [14, 21] also investigated as an *in-vivo* generator [33]	0	0	0
^{212}Bi	Targeted alpha therapy [14, 21]	0	0	0
^{213}Bi	Theranostic (targeted alpha therapy + SPECT) [14, 20, 21]	0	0	0
^{211}At	Targeted alpha therapy for thyroid cancers [14, 20, 21]	0	0	0
^{211}Rn	Parent nuclide for At-211 [34]	0	0	0
^{223}Ra	Alpha therapy for bone metastases [14, 21, 35]	4	4[i]	0
^{224}Ra	Alpha therapy for tuberculosis, ankylosing spondylitis [36]; Parent nuclide for Pb-212 [14]	0	0	0
^{225}Ac	Targeted alpha therapy for prostate, brain and neuroendocrine cancers [14, 20, 21]	2	2[j]	0
^{227}Ac	By product of Ac-225 production [21, 37]	0	0	0
^{227}Th	Targeted alpha therapy [14, 21, 38]	0	0	0

[a] CCRI(II)-K2.P-32 comparisons planned in 2002 and 2005 but abandoned. The ESIR comparison BIPM.RI(II)-K5.P-32 will be soon opened.
[b] A CCRI(II)-K2.Sr-89 held in 2001 but the DoEs are now outdated. The ESIR comparison BIPM.RI(II)-K5.Sr-89 will soon be opened.
[c] A CCRI(II)-K2.Sr-90 held in 1998 but the DoEs are now outdated. The ESIR comparison BIPM.RI(II)-K5.Sr-90 will soon be opened.
[d] A CCRI(II)-K2.Y-90 held in 2003 [51] and there is only one BIPM.RI(II)-K1.Y-90 result from PTB. The ESIR comparison BIPM.RI(II)-K5.Y-90 will soon be opened.
[e] One result from NPL measured with the SIR in 2011.
[f] The SIRTI comparison BIPM.RI(II)-K4.Sm-153 will soon be opened.
[g] One submission from CMI. An EURAMET.RI(II)-K2 comparison is planned.
[h] The ESIR comparison BIPM.RI(II)-K5.Er-165 will soon be opened.
[i] Recent BIPM.RI(II)-K1.Ra-223 results from NPL and PTB in 2014, LNE-LNHB in 2018 and POLATOM in 2021.
[j] Recent BIPM.RI(II)-K1.Ac-225 results from PTB in 2019 and POLATOM in 2021.

Table 4. Radionuclides for *in vitro* diagnostics.

Radionuclide	Example uses	Participations in BIPM services	Number of current DoEs	Number of CMCs
^{24}Na	For studies of electrolytes within the body [14]	2	2	18
^{32}P	Viroid RNA for hybridization studies [39]	0	0[a]	25
^{35}S	Radiolabel proteins [40]	0	0[b]	1
^{42}K	Used in release assays [41]	0	0	6
^{51}Cr	Used to label red blood cells [14]	11	9	56
^{59}Fe	Used in studies of iron metabolism in the spleen [14]	10	11	34
^{57}Co	*In-vitro* diagnostic kits [14]	15	5	81
^{75}Se	Used to study the production of digestive enzymes [14]	4	0[c]	37
^{125}I	Used in radioimmuno-assays to show the presence of hormones [14]	0	22	36
^{131}I	*In vitro* human epidermis model [42]	15	17	52
^{191}Pt	Study cervical carcinoma cell line [43]	0	0	0

[a] CCRI(II)-K2.P-32 comparisons planned in 2002 and 2005 but abandoned. The ESIR comparison BIPM.RI(II)-K5.P-32 will be soon opened.
[b] The ESIR comparison BIPM.RI(II)-K5.S-35 will be soon opened.
[c] All results from CCRI(II)-K2.Se-75 and BIPM(II)-K1.Se-75 are now outdated.

- The number of current degrees of equivalence (DoEs are valid for a period of 20 years) from any [CCRI(II), RMOs or BIPM(II)] key comparison,
- The number CMCs claimed by NMIs (supported by comparison results or other means).

5. The status of primary standards

A measurement of the activity content of a radiopharmaceutical can be considered as fit for purpose if the measurement uncertainty in the clinic is on the order of a few percent [2]. This level of accuracy is implied in product specifications described in the Pharmacopoeia [44] or in the marketing authorization under pharmaceutical regulations; a tolerance (upper and lower bounds) of 10% is common. The accuracy needed for the primary standards to which these measurements are referred is therefore around 1%, to allow for the increase in uncertainty along the measurement chain to the clinic or manufacturer.

The results from all international comparison exercises are recorded in the KCDB and most have also been published in the *Metrologia* Technical Series such as the recently published comparison reports for ^{241}Ac [45] and ^{223}Ra [46]. For this article, the SIR results, $A_{e,i}$ (see equation (2)), from comparisons of each radionuclide have been extracted from the SIR digital database [47] and normalized to the KCRV for that radionuclide such that

$$y_i = \frac{A_{e,i}}{\mathrm{KCRV}}. \tag{4}$$

The plots of y_i given in section 5 display standard uncertainties $u(y_i)$ and are dominated by the uncertainty in the primary standardizations (the contribution from the SIR and SIRTI are generally lower).

An objective measure of 'fitness for purpose' is not straightforward to define. It could be argued that, if a comparison exercise shows that the national standard from a metrology institute departs more than 1% from the KCRV, primary standards are not fit for purpose globally as measurements in that participating country are discrepant. The results may be used to investigate the cause of any discrepancy and the national standard subsequently improved. Any corrections made are not reflected in the results reported for the comparison exercise.

For the purposes of this review, we will define primary standards as fit for purpose if an NMI can realize a primary standard with a standard uncertainty of between 1% or less and 5%, depending on the radionuclide as evidenced by results of international comparison exercises or other appropriate demonstrations. The statistical test for conformity is taken from JCGM 106 [48]—in essence, each measured value is treated as an estimate of the KCRV. Each measurement result is characterized by a normal probability distribution with a mean equal to the measured value and a standard deviation equal to its associated standard uncertainty. These distributions are combined to form a normal distribution for the aggregation. The standard deviation of this probability distribution is a measure of how well the primary standards can be realized.

Given a relative tolerance limit T that could be accepted by the user of a given primary standard, JCGM 106 defines the conformance probability p_c as a function of the estimations of the expectation value η_m and the standard uncertainty u_m from the measurement y_i. The expectation value and standard uncertainty are given by

$$\eta_m = \frac{1}{n}\sum_{i=1}^{n} y_i \tag{5}$$

and

$$u_m^2 = \frac{1}{n(n-1)}\sum_{i=1}^{n}(y_i - \eta_m)^2. \tag{6}$$

The conformance probability (that primary standards are consistent with the defined relative tolerance T), again assuming normality, is calculated as

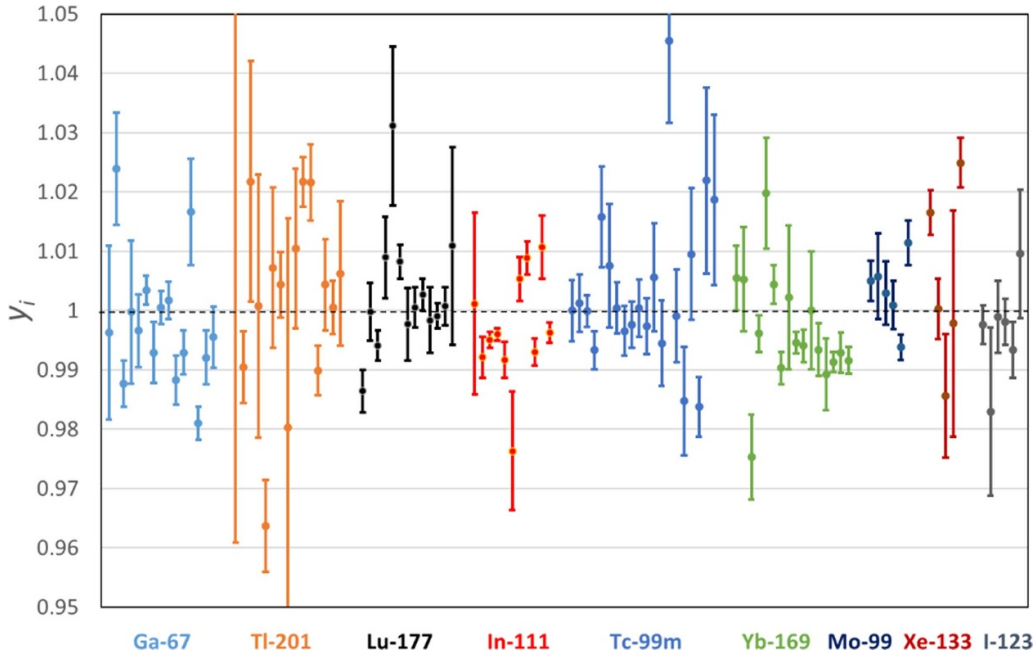

Figure 3. Equivalence of primary standards used for SPECT. For a given radionuclide, data points are sorted in chronological order of SIR submissions. Error bars represent ± 1 standard uncertainty about the measured value.

$$p_c = \frac{1}{2}\left[\mathrm{erf}\left(\frac{\sqrt{2}T\eta_m}{u_m}\right) - \mathrm{erf}\left(-\frac{\sqrt{2}T\eta_m}{u_m}\right)\right], \qquad (7)$$

where erf() is the error function.

This calculation permits the assessment of the risk $1 - p_c$ that the end-user of the standardized radionuclide solution takes, bearing in mind the tolerance level T for treatment or diagnosis. As previously mentioned, this assessment does not consider what could happen in the traceability chain between the NMI and the hospital; the aim of the calculation is to help the NMIs identify where work may be needed to improve primary standards or to realize new standards. The results are the best case (a picture taken at the primary standardization step) and measurement uncertainties will be larger at the clinical level.

The results from the comparison exercises are given in the following subsections, categorized according to the medical application.

5.1. Radionuclides used for SPECT

Radionuclides used for SPECT are standardized using proportional counters or liquid scintillation devices implementing 4π coincidence or anti-coincidence techniques, or ionization chambers previously calibrated by these primary standardization techniques. The comparison values y_i are shown in figure 3 and the conformance probabilities are reported in table 5.

In terms of the number of administrations per year, ^{99m}Tc dominates nuclear medicine—it is readily available worldwide using a ^{99}Mo/^{99m}Tc generator, the energy (140 keV) of the gamma ray emitted is optimum for imaging, and it can be used to label a wide range of molecules with various physiological functions. However, due to its short half-life of about 6 h, it can be difficult to support the realization of a primary standard of this radionuclide through comparisons. Nevertheless, there have been 22 submissions (including 10 results carried out with the SIRTI) to comparison exercises (see figure 3). Results are in reasonable agreement within the $\pm 5\%$ tolerance expected by the practitioner leading to a non-conformance probability lower than 0.001 (see table 1). The same conclusion can be drawn for ^{67}Ga, ^{177}Lu, ^{111}In, ^{169}Yb, ^{99}Mo and ^{123}I. However, ^{201}Tl and ^{133}Xe do not achieve the same conformance level. Further standardizations for these radionuclides would be valuable to give additional confidence and to ensure long-term maintenance of the capability in the metrology community. To date, there has not been an international comparison for ^{47}Sc, ^{67}Cu, ^{111}Ag, ^{153}La, ^{155}Tb, ^{161}Tb, ^{167}Tm, ^{166}Dy, ^{166}Ho, ^{186}Re and ^{213}Bi actively studied from the theranostic perspective.

Table 5. Conformance probability of primary standards used for SPECT calculated for several tolerance intervals T.

Radionuclide	$T = 1\%$	$T = 2\%$	$T = 3\%$	$T = 4\%$	$T = 5\%$
Ga-67	64.1%	93.4%	99.7%	100.0%	100.0%
Tl-201	37.9%	67.7%	86.2%	95.2%	98.7%
Lu-177	65.4%	94.1%	99.5%	100.0%	100.0%
In-111	70.3%	96.3%	99.8%	100.0%	100.0%
Tc-99m	53.1%	85.3%	97.0%	99.6%	100.0%
Yb-169	69.3%	95.9%	99.8%	100.0%	100.0%
Mo-99	85.0%	99.6%	100.0%	100.0%	100.0%
Xe-133	44.9%	76.7%	92.6%	98.3%	100.0%
I-123	65.7%	94.2%	99.6%	100.0%	100.0%

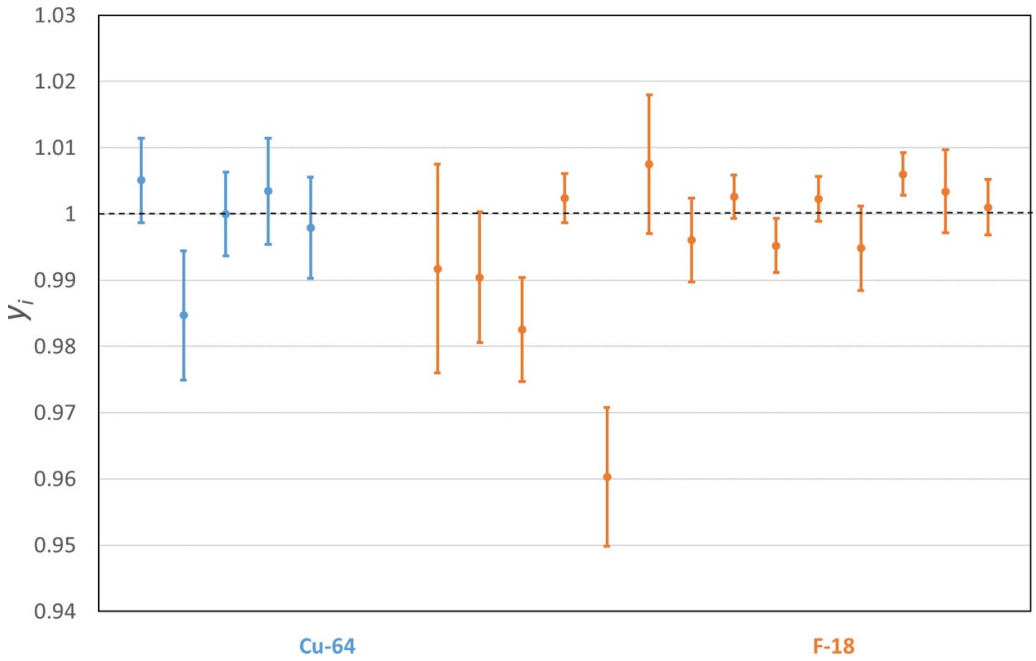

Figure 4. Equivalence of primary standards used for PET. For a given radionuclide, data points are sorted in chronological order of SIRTI submissions. Error bars represent ± 1 standard uncertainty about the measured value.

Table 6. Conformance probability of primary standards used for PET calculated for several tolerance intervals T.

Radionuclide	$T = 1\%$	$T = 2\%$	$T = 3\%$	$T = 4\%$	$T = 5\%$
Cu-64	74.6%	97.8%	99.9%	100.0%	100.0%
F-18	58.6%	89.7%	98.6%	99.9%	100.0%

5.2. Radionuclides used for PET

Results are available for two β^+ decaying radionuclides being used for PET: ^{64}Cu and ^{18}F. Comparison studies for ^{64}Cu, with a half-life of about 13 d, have been carried out using the SIR. The SIRTI has been used to compare standards of ^{18}F (half-life 1.8 h). The comparison values y_i are shown in figure 4 and the conformance probabilities are reported in table 6. Results for these two PET radionuclides are in reasonable agreement and a tolerance of $\pm 4\%$ can be established, leading to a non-conformance probability lower than 0.001 (see table 6).

No comparison exercises have been carried out for other PET radionuclides including proposed radionuclides such as ^{44}Sc and ^{152}Tb. Measurements of these radionuclides can be assumed to rely on the MMM and on published nuclear decay data; further studies of these radionuclides would be useful to confirm conformity.

5.3. Radionuclides used for therapy

Radionuclides used for therapy are standardized using proportional counters or liquid scintillation devices implementing 4π coincidence or anti-coincidence techniques, or ionization chambers previously calibrated by these primary standardization techniques. Proportional counters are used mostly for ^{131}I and ^{177}Lu while liquid scintillation techniques, including CIEMAT/NIST and TDCR methods, are used mostly for ^{153}Sm, ^{223}Ra, ^{90}Y and ^{89}Sr. The results from comparison studies y_i are shown in figure 5 for ^{131}I, ^{177}Lu, ^{153}Sm, and ^{223}Ra. The related conformance probabilities are reported in table 7. Results for these therapeutic radionuclides are in good agreement, and a lower tolerance than that for diagnostic radionuclides can be set. Indeed, a tolerance of $\pm 3\%$ can be reasonably established for ^{131}I and ^{153}Sm, which leads to a non-conformance probability lower than 0.001 (see table 7). However, a tolerance of $\pm 4\%$ should be considered for ^{177}Lu used for both therapy and diagnostic studies.

The recent results obtained for the alpha emitter ^{223}Ra are promising but more equivalence data must be produced to improve the significance of this analysis.

For the pure beta radionuclides, such as ^{90}Y and ^{89}Sr, even if key comparisons were organized independently from the BIPM centralized services, the results cannot be linked afterwards to the SIR to ensure the permanence of the KCRV. This consideration underlines the crucial need to develop the ESIR to make a better assessment of equivalence for β-therapy standards (^{90}Y, ^{89}Sr, ^{47}Sc and ^{169}Er) and to help improve equivalences of α-therapy radionuclides such as ^{225}Ac, ^{149}Tb and ^{211}At. The ESIR will also be useful to compare standards of Auger-therapy radionuclides ^{165}Er and ^{135}La which show strong promise for future cancer treatments [49].

5.4. Radionuclides used for in-vitro diagnostic tests

Radionuclides used for *in-vitro* diagnostic are standardized using proportional counters or liquid scintillation devices implementing 4π coincidence or anti-coincidence techniques, or ionization chambers previously calibrated by these primary standardization techniques. For ^{57}Co, ^{131}I, ^{51}Cr, ^{59}Fe, ^{75}Se and ^{24}Na, comparison values y_i are shown in figure 6 and

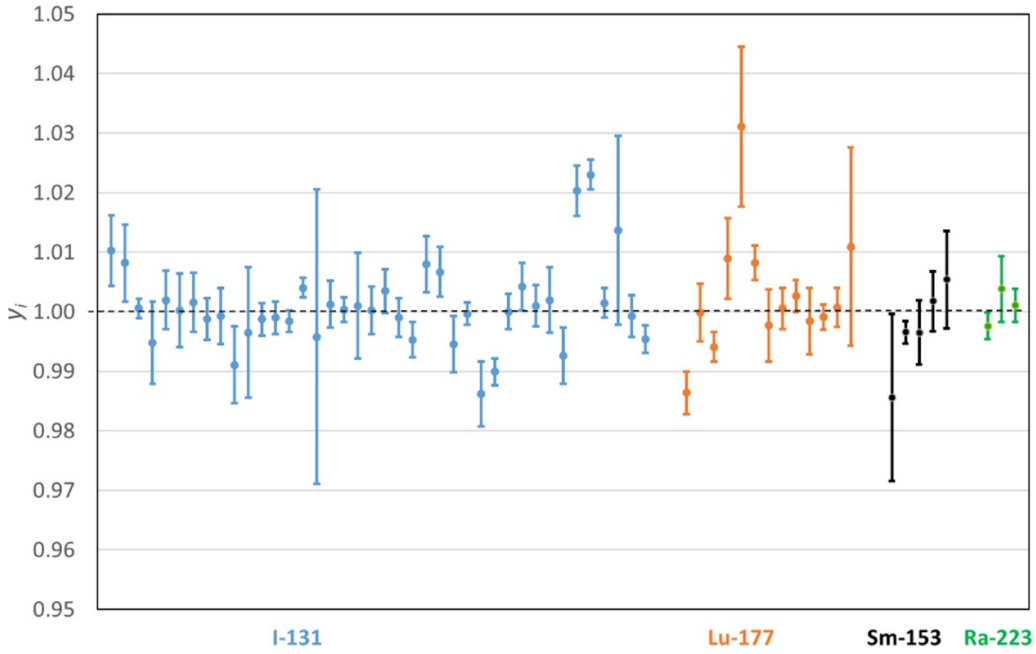

Figure 5. Equivalence of primary standards used for therapy. For a given radionuclide, data points are sorted in chronological order of SIR submissions. Error bars represent ± 1 standard uncertainty about the measured value.

Table 7. Conformance probability of primary standards used for therapy calculated for several tolerance intervals.

Radionuclide	$T = 1\%$	$T = 2\%$	$T = 3\%$	$T = 4\%$	$T = 5\%$
I-131	83.8%	99.5%	100.0%	100.0%	100.0%
Lu-177	65.4%	94.1%	99.85%	100.0%	100.0%
Sm-153	76.0%	98.1%	100.0%	100.0%	100.0%
Ra-223	99.3%	100.0%	100.0%	100.0%	100.0%

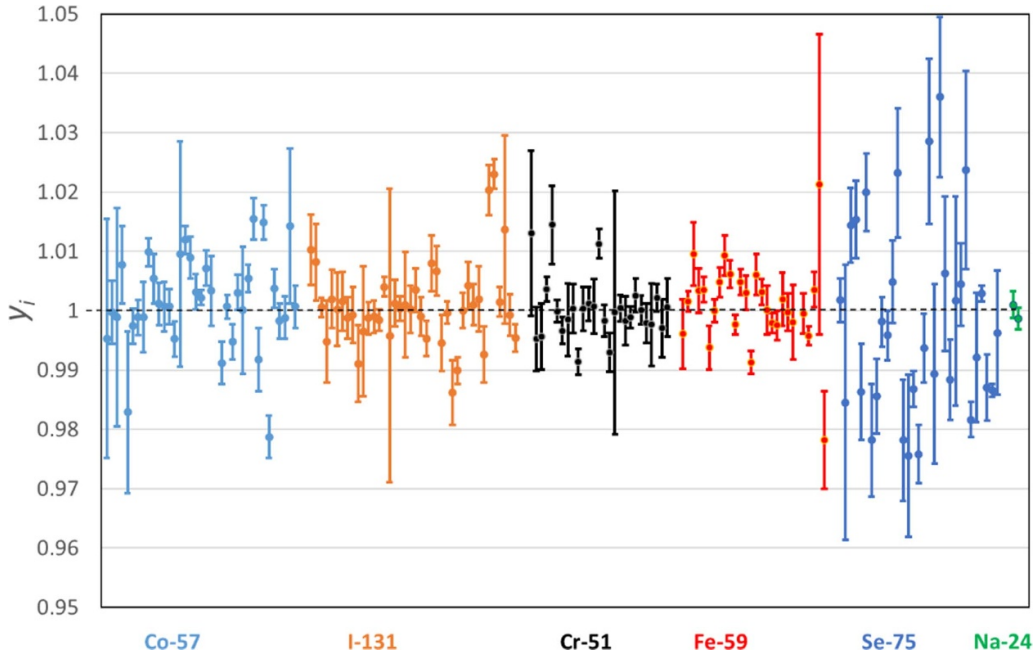

Figure 6. Equivalence of primary standards used for *in-vitro* diagnostics. For a given radionuclide, data points are sorted in chronological order of SIR submissions. Error bars represent ± 1 standard uncertainty about the measured value.

Table 8. Conformance probability of primary standards implied in *in-vitro* diagnostics for several tolerance intervals *T*.

Radionuclide	$T = 1\%$	$T = 2\%$	$T = 3\%$	$T = 4\%$	$T = 5\%$
Co-57	42.0%	73.2%	90.3%	97.3%	99.7%
I-131	83.8%	99.5%	100.0%	100.0%	100.0%
Cr-51	94.0%	100.0%	100.0%	100.0%	100.0%
Fe-59	55.5%	87.4%	97.8%	99.8%	100.0%
Se-75	45.7%	77.7%	93.2%	98.5%	99.8%
Na-24	100.0%	100.0%	100.0%	100.0%	100.0%

the conformance probabilities are reported in table 8. Results for ^{51}Cr and ^{131}I are in good agreement and a low tolerance of $\pm 2\%$ or $\pm 3\%$ can be reasonably established (non-conformance probability lower than 0.001 as seen in table 8). More discrepant values are observed for ^{59}Fe, ^{57}Co and ^{75}Se, and a larger tolerance of $\pm 5\%$ or $\pm 6\%$ should be considered (further studies of these radionuclides may be useful, particularly for ^{57}Co which is also used in reference materials to calibrate high-resolution gamma spectrometers).

The results for ^{24}Na are promising but further standardizations for these radionuclides would be invaluable to improve the significance of this result. The equivalence of the electron-capture decaying ^{125}I was studied through K2 comparisons, but never linked to the SIR due the very low energy of emitted x- and gamma-rays. ^{35}S and ^{32}P are also commonly used for *in vitro* diagnostics. However, no international comparison result has been published due to their pure beta decay and radiochemical issues to separate impurities [50]. Again, the development of the ESIR is a very welcome addition to enhance the traceability of these radionuclides.

6. Conclusions

The radionuclide metrology community has established a robust international system to cross-check primary standards of radionuclides used in nuclear medicine and realized in different countries through comparison exercises. Some of the exercises rely on a set of highly stable, high-precision transfer instruments, which enable comparisons over time as well as between metrology institutes. Analyses of results from these comparison exercises have shown that primary standards have been realized at an accuracy that is fit for purpose for many of the radionuclides used for diagnostics and therapy.

There remain, however, radionuclides for which there have been no comparisons, and some for which there is no evidence from published data on the KCDB that show that primary standards have been realized. This absence particularly applies to radionuclides identified as candidates for future radiopharmaceutical products; the challenge for the radionuclide metrology community is to work with radiopharmaceutical manufacturers to prioritize which radionuclides should be studied. This review is offered as an input to decisions by the CCRI on priorities for future comparison exercises and for recommendations for the development of new primary standards.

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