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Preparation of radioactive phantoms with an activity traceable to international standards.

ADVANCED

TECHNICAL LEVEL

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Forward

The intended aim of this Good Practice Guide is to assist users in the preparation of radioactive phantoms (body analogues), ensuring that the uncertainty on the activity dispensed to the phantom can be estimated and that the activity measurement is traceable to a national standard of radioactivity. Although the methods in this guide do not guarantee a specific accuracy for the measurement of activity in the phantom, in most cases, they will provide the smallest uncertainty routinely achievable with a given measurement device in an end-user measurement.

We hope this guide will prove useful for a wide range of users in clinical, pre-clinical, academic, and industrial settings where there is the need to prepare an object containing a radioactive solution with a traceable measurement of activity.

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List of Terms

BIPM	Bureau International des Poids et Mesures (International Bureau of Weights and Measures)
BG	Background
c_i	Sensitivity coefficient. Provides information on how an output measurement is affected by the given inputs.
CF	Calibration Factor (also called dial setting, calibration setting) - in the context of radionuclide calibrators
DI	Designated Institute
HCl	Hydrochloric Acid
n.c.a	Non-carrier added
NMI	National Measurement Institute
NPL	National Physical Laboratory
PET	Positron Emission Tomography
QC	Quality Control
SPECT	Single Photon Emission Computerised Tomography
RC	Radionuclide calibrator
RRC	Reference Radionuclide Calibrator
SD	Standard Deviation
SSIC	Secondary Standard Ionisation Chamber
SSRC	Secondary Standard Radionuclide Calibrator
$u(x_i)$	Standard uncertainty. Corresponds to the uncertainty value divided by the divisor. The divisor depends on the probability distribution
$u_i(y)$	Contribution to combined standard uncertainty. $u_i(y) = u(x_i) \times c_i$
u_c	Combined standard uncertainty.
U	Expanded uncertainty. $U = k \times u_c$ where k corresponds to the coverage factor. For a normal distribution, k = 1,2 and 3 correspond to a probability of approximately 68%, 95% and 99.7 % respectively.
UTC	Coordinated Universal Time

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Chapter 1

Introduction

Phantoms containing a radioactive solution are used extensively in nuclear medicine and related fields for Quality Control (QC), calibration, assessment of image quality and characterisation of Single Photon Emission Computerised Tomography (SPECT) and Positron Emission Tomography (PET) systems. Phantoms are available commercially, or may be a custom design, and can provide a range of different phantom geometries, often with smaller inserts to provide specific activity distributions (1–7).

In all use cases there is a requirement to know the activity contained within the phantom, to allow appropriate radiation protection procedures to be used. When the phantom is used as part of any form of quantitative calibration or measurement then the activity in the phantom should be measured as accurately as possible, include an estimate of the uncertainty in the measurement and the measurement should be traceable to an appropriate standard of radioactivity. This necessitates the use of instrumentation capable of measurements that are traceable to international standards (8–11) and careful consideration of all sources of uncertainty in the preparation of the phantom, enable meaningful comparison between measurements from different centres and systems.

Radionuclide calibrators (RC) are the most common instrumentation used for activity assay before administration of activity to patients and for phantom preparation. This instrument, when used and maintained properly, can achieve the levels of accuracy required to fill phantoms for a range of applications. Several published studies reported the results of intercomparison results showing the variability in the activity measurements using RC for different centres. These studies, which have been performed for different radionuclides, show the need for standardisation and traceability for measurements using radionuclide calibrators (12–20). A study from Bailey et al. (18), showed the impact on quantitative PET imaging when the calibration setting (also known as dial setting or calibration factor) in the radionuclide calibrator for ^{68}Ga was incorrect for the geometry used. This led to the underestimation of the Standardised Uptake Values (SUV) by up to 23 %. Quantitative imaging comparison exercises between different sites using ^{177}Lu and highlighted the need for traceability for radionuclide calibrator measurements (21,22). In addition to this, a multi-centre dosimetry study using radioiodine activities traceable to standards highlighted the importance of using equipment that is calibrated and traceable to primary standards of radioactivity (23). Several authors have reported the need of an appropriate quality assurance and validation of radionuclide calibrators for relevant geometries for clinical imaging and the need for verification of the calibration setting for each radionuclide and geometry of interest used in clinical practice (18,20,24,25).

The purpose of this work is to provide guidance on the preparation of liquid radioactive phantoms with an activity traceable to international standards used in quantitative imaging. Calibration of imaging equipment in nuclear medicine is an important step to convert counts in the image to activity in becquerel (Bq). Cumulated activities can be used to calculate absorbed

doses to organs at risk and organs of interest in molecular radiotherapy, and therefore the calibration of the system must be performed using a traceable radioactive source and the uncertainties must be known. Incorrect calibration of imaging systems can result in an underestimation or overestimation of the calculated dose.

Chapter 2

Traceability

Measurement traceability is defined by the international vocabulary of metrology as the "property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty" (26), i.e. the measurements performed within the unbroken chain are traceable and comparable and uncertainties must be reported at each stage to enable comparison.

In nuclear medicine, a primary standard is developed for each individual radionuclide and often transferred to secondary standards (such as ionisation chambers) due to the difficulty and expenses of developing primary standards. The primary standards are developed and maintained by National Measurement Institutes (NMIs) and Designated Institutes (DIs). Secondary standards are also often maintained by NMIs or DIs, who participate in international measurement comparison exercises to establish their traceability and equivalence to international standards. Figure 1 illustrates the traceability and equivalence between NMIs and the end users. The measurement results of the intercomparison exercises and respective uncertainties are reported to the International Bureau of Weights and Measures (BIPM) (9).

The preparation of phantoms traceable to international standards requires that the equipment used to measure the activity dispensed to the phantom is calibrated against primary standards for the radionuclide of interest (i.e., having traceability for one radionuclide does not make the radionuclide calibrator traceable for all radionuclides).

Different methods can be used to achieve traceability for radionuclide calibrators. A sample of the radionuclide and geometry of interest may be sent for calibration to an NMI or designated institute (DI) (24,27) or a calibrated sample can be received from an NMI, DI or radiopharmaceutical supplier (24,25). The NMI, DI and supplier must be able to demonstrate traceability for the radionuclide being measured and the reported uncertainty for the measured activity must be equivalent to those achieved with a SSRC or RRC (25). The methodology chosen to ensure traceability will depend on local legislation or on local availability. In this document, the equipment and methodology for the preparation of phantoms with a known-activity traceable to standards are described. An important step for traceability and to understand the measurement is to estimate the measurement uncertainty. Guidance is also provided on the estimation of uncertainties and when applicable assumptions are made to simplify this process.

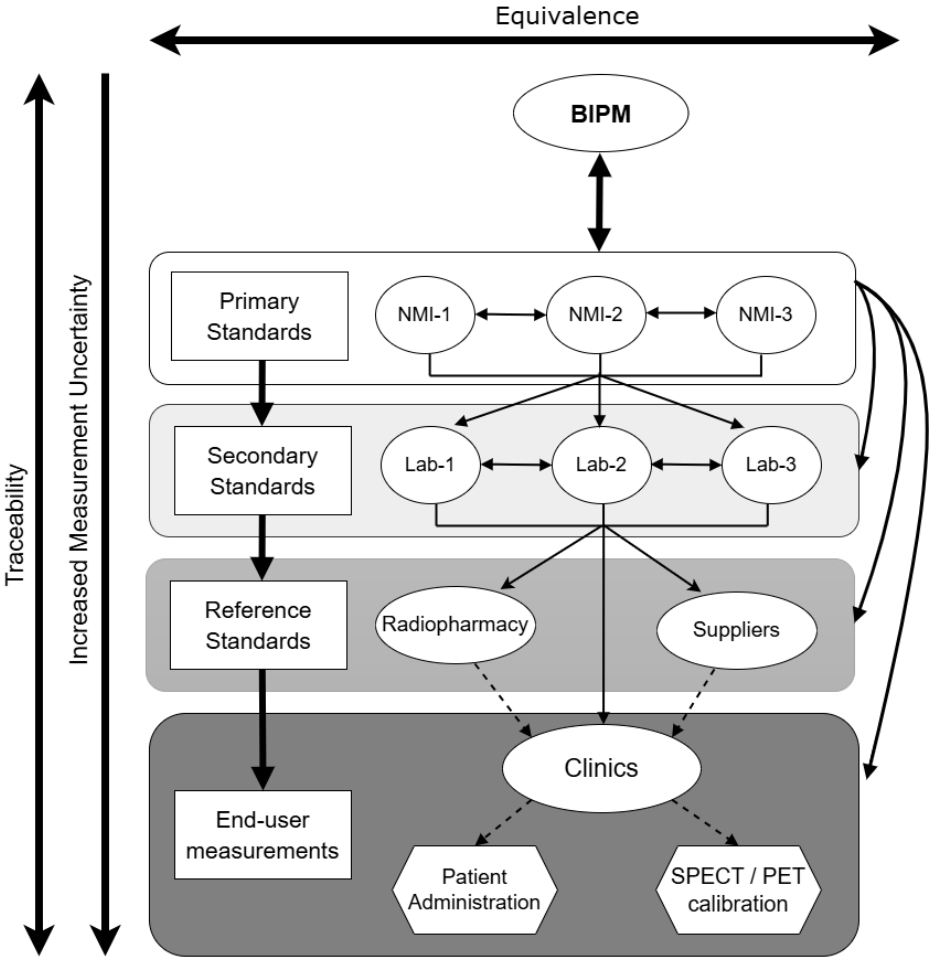

Figure 1: *Example of traceability and Equivalence Chains Diagram. NMI-1, NMI-2 and NMI-3 correspond to different NMIs participating in international intercomparison exercises. Lab-1, Lab-2 and Lab-3 correspond to national measurement institutes, designated institutes or other laboratories that provide secondary standards.*

2.1. Measurement uncertainty

The guide to the expression of uncertainty in measurement (GUM) provides a framework for the evaluation and expression of uncertainties in measurement (28). In this work the principles of the GUM will be followed and the law of propagation of uncertainty (LPU) will be applied when estimating uncertainties for total activity dispensed to a phantom or a container.

Assumptions can be made to facilitate the estimation of uncertainties, and these will be made when appropriate.

There are two ways of estimating uncertainties: Type A evaluations and Type B evaluations. In Type A evaluations, uncertainties are estimated using statistical methods. In Type B evaluations, the uncertainties are estimated from non-statistical methods, such as calibration certificates, published information, manufacturer's specifications, and others (29). The individual standard uncertainties are combined mathematically using the LPU as shown in equation (1).

$$u_c^2(y) = \sum_{i=1}^{N} c_i^2 \, u_i^2(x_i) + 2 \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} c_i \, c_j \, u\,(x_i, x_j) \tag{1}$$

A simplified version of LPU can be used if the input quantities are not correlated, since the covariance term in equation (1) becomes zero and therefore the equation can be simplified as shown in equation (2).

$$u_c^2(y) = \sum_{i=1}^{N} c_i^2 \, u_i^2(x_i) \tag{2}$$

The sensitivity coefficients (c_i) in equations (1) and (2) can also be written in terms of partial derivatives.

$$u_c^2(y) = \sum_{i=1}^{N} \left(\frac{\partial y}{\partial x_i}\right)^2 u_i^2(x_i) \tag{3}$$

In this document the full and simplified versions of the LPU will be used. The nomenclature in equations 1 to 3 will be used and the output variable (y) and input variables (x_i) will be replaced with the variable names relevant to this document and to the measurement models being analysed. Additional information and examples on how to estimate and propagate uncertainties can be found in the GUM (28).

Chapter 3

Materials

3.1. Radionuclide calibrators

Radionuclide calibrators (RC) are commonly used in nuclear medicine for the measurement of activity before patient administration and for the preparation of radioactive phantoms used to calibrate, commission, and validate nuclear medicine imaging systems. The manufacturer calibration settings on a RC are defined for each radionuclide, for a specific and well-defined geometry measured in a standard position. The RC response is highly dependent on the radionuclide and measurement geometry used (i.e. vial type, material of the container, volume of solution), and therefore a RC should be calibrated for individual radionuclides and for the geometries of interest (24) to improve measurement accuracy.

The user should ensure the RC has previously been calibrated using a traceable route for the radionuclide of interest in a well-defined and controlled geometry. If this is not guaranteed, a traceable standard should be used to check the calibration setting for the geometry used and calibrate the instrument if necessary. Measurement geometries can vary significantly between users and to achieve traceability for phantom preparation it is essential that measurements are performed in an appropriate geometry. Commonly, vials and syringes are used to perform such measurements in the radionuclide calibrator.

The user is also responsible to ensure a robust QC programme for the RC with appropriate records and respective control charts. The maintenance, correct use of a radionuclide calibrator and calibration of radionuclide calibrators for different geometries is covered in (24,25,27,30) and will not be discussed further in this document.

3.2. Balances

A calibrated balance should be used for the preparation of phantoms where it is necessary to know the activity per unit mass, for example when dispensing from stock solution or to improve the accuracy of the activity dispensed to the phantom. The balance used shall have enough capacity and resolution to weigh the empty and full containers accurately. The correct use and maintenance of balances is covered in (31,32). Calibrated volumetric dispensers can also be used but are not recommended for smaller volumes due to the larger uncertainties associated with dispensing volumetrically rather than gravimetrically (27). For larger volumes (e.g., when preparing a carrier solution), a volumetric dispenser can be used but care should be taken to incorporate uncertainties when using this method.

3.3. Carrier solutions and radionuclides

A carrier solution with an appropriate chemistry should be used to ensure the stability and homogeneity of the radioactive solution. The carrier solution consists of an acidic or basic solution with the presence of an inactive element, with similar properties to the radionuclide of interest. In radioactive solutions with unsuitable chemistries, the activity might not be homogeneously distributed, stick to the walls of the vials/containers/phantoms, or evaporate

from the solution (33). This can lead to a non-homogeneous distribution of activity in the phantom and consequently errors in the activity measurement.

In addition to the carrier solution, where practical and possible, non-carrier added (i.e., free of radionuclide impurities) radionuclides are recommended. In this context, non-carrier added is used to define the method of production of the radionuclides (i.e., radionuclides produced by a direct method of irradiation are also referred to as non-carrier added radionuclides). The terms non-carrier added and carrier solution to dilute radioactive solutions should not be confused. The use of radiopharmaceutical compounds (e.g., radiolabelled peptides, microspheres, or colloidal solutions) should be avoided. The presence of radiopharmaceutical compounds in the solution can make the radioactive solution stick to the walls of the containers and lead to the same errors described above. A list of suggested carrier solutions for commonly used radionuclides are presented in Appendix 1 and an example of the process to prepare a carrier solution for ^{177}Lu is described in Appendix 2. Additional guidance on the preparation of carrier solutions can be found in UKAS Lab Guide 26 (33).

Chapter 4

Methods for the preparation of phantoms with a total activity traceable to national standards

In this section, different methodologies are described for the preparation of a phantom with a traceable known total activity and estimation of respective uncertainty. General advice on preparing radioactive solutions is also available in UKAS Lab Guide 26 (33) and Monographie BIPM (34). The methodologies consider in this work cover,

4.1 Radionuclide calibrator measurements using a traceable calibration setting for a vial.

4.2 Radionuclide calibrator measurements using a traceable calibration setting for a syringe.

4.3 Radionuclide calibrator measurements using a traceable calibration setting for a vial and a calibrated balance.

The main difference between methods 4.1 and 4.2 is the geometry used for the measurements of activity in the radionuclide calibrator. In method 4.1, a vial is used and in method 4.2, a syringe is used for the activity measurements. In method 4.3 the solution is dispensed gravimetrically to the phantom from the container measured in the radionuclide calibrator and depending on the accuracy of the balances and the radionuclide calibrator used, often results in lower uncertainties compared to methods 4.1 and 4.2 (which do not require the use of a balance).

4.1. Radionuclide calibrator measurements using a traceable calibration setting for a vial

In this section, the process to fill a phantom (of an arbitrary size or shape) with a radioactive solution is described. The total activity in the phantom is calculated using a traceable calibration setting for a vial geometry and a syringe is used to transfer the solution from the vial to the phantom. The vial and syringe and vial will be measured on the radionuclide calibrator. Any calibration setting can be used for the syringe measurements as these will be used to calculate the ratio of residue activity left in the vial, however using a common calibration setting to measure the vial and syringe may help reduce errors. Background measurements (i.e., without sources in or near the chamber) should also be measured in the same calibration setting as the vial. It is also recommended to use the same clock for all the measurements with an accuracy of at least 1 second. An example using this method to fill a cylindrical phantom is presented in Appendix 3.

Phantom preparation and radionuclide calibrator measurements

1. Fill the initial vial with the radionuclide solution to be dispensed (ensure this matches the volume and carrier solution for the calibration setting geometry).
2. Measure the background (b_1).

3. Measure the initial full vial in the radionuclide calibrator using the appropriate calibration setting and note the time of measurement (a_1, t_1).
4. Using a syringe, remove the solution from the vial. Take care to remove as much solution from the vial as possible.
5. Measure the background (b_2) on the radionuclide calibrator.
6. Measure full syringe in the radionuclide calibrator and note the time of measurement (a_2, t_2).
7. Dispense activity in the syringe to the phantom.
8. After dispensing the solution to the phantom, refill the syringe with carrier to the same volume as before dispensing to the phantom.
9. Measure the background (b_3) on the radionuclide calibrator.
10. Measure the empty syringe in the radionuclide calibrator and note the time of measurement (a_3, t_3).
11. Using a clean syringe refill the empty vial with carrier to the same volume as the initial vial.
12. Measure the background (b_4) on the radionuclide calibrator.
13. Measure the residue vial and note the time of measurement (a_4, t_4).
14. a_1, a_2, a_3 and a_4 should be corrected for the corresponding BG measurements (b_1, b_2, b_3 and b_4) and decay corrected to a common reference time (t_{ref}) using equation (4).

$$A(t_{ref}) = (a_i - b_i)e^{-\lambda(t_{ref} - t_i)} \tag{4}$$

15. The total activity in the phantom (A_{ph}) can be calculated from the decay and background corrected activities (A_1 to A_4) using equation (5).

$$A_{Ph}(t_{ref}) = \left(A_1(t_{ref}) - A_4(t_{ref})\right).\left(1 - \frac{A_3(t_{ref})}{A_2(t_{ref})}\right) \tag{5}$$

Uncertainty estimation

16. In this case the LPU (Eq. 1) may be applied to estimate the uncertainty in $A_{ph}(t_{ref})$ With the assumption that the half-life ($t_{1/2}$) of the radionuclide >> ($t_{ref} - t_1$) and $t_{1/2}$ >> ($t_1 - t_2$), and therefore the uncertainty associated with these components approximates to zero and also the correlation between these terms will also approximate to zero, the combined uncertainty for the total activity ($u(A_{ph}(t_{ref}))$ dispensed to the phantom can be estimated using equation (6).

$$u\left(A_{ph}(t_{\mathrm{ref}})\right)^2 = \sum_{i=1}^{4}\left[\left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial a_{\mathrm{i}}}\right)^2 u\,(a_{\mathrm{i}})^2 + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial b_{\mathrm{i}}}\right)^2 u\,(b_{\mathrm{i}})^2 + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial t_{\mathrm{i}}}\right)^2 u\,(t_{\mathrm{i}})^2\right] + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial \lambda}\right)^2 u\,(\lambda)^2 + 2\sum_{i=1}^{3}\sum_{j=2}^{4}\left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial A_{\mathrm{i}}}\right)\left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial A_{\mathrm{j}}}\right)u(A_{\mathrm{i}}, A_{\mathrm{j}}) \tag{6}$$

17. The measurements a_1, a_2, a_3, a_4, and the corresponding background measurements (b_i) are correlated when using the same calibration setting and radionuclide calibrator. Equation (7) is a simplification of equation (6) and considers the correlations.

$$u(A_{\mathrm{ph}}(t_{\mathrm{ref}}))^2 = \sum_{i=1}^{4}\left[\left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial a_{\mathrm{i}}}\right)^2 u\,(a_{\mathrm{i}})^2 + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial b_{\mathrm{i}}}\right)^2 u\,(b_{\mathrm{i}})^2 + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial t_{\mathrm{i}}}\right)^2 u\,(t_{\mathrm{i}})^2\right] + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial \lambda}\right)^2 u\,(\lambda)^2 + A_{\mathrm{ph}}(t_{\mathrm{ref}})^2 u\,(CF)^2 + A_{\mathrm{ph}}(t_{\mathrm{ref}})^2 u\,(A_{\mathrm{repro}})^2 + A_{\mathrm{ph}}(t_{\mathrm{ref}})^2 u\,(A_{\mathrm{linear}})^2 \tag{7}$$

Where, $u(a_i)$ and $u(b_i)$ correspond to the statistical uncertainty, $u(\lambda)$ is the uncertainty on the decay constant of the radionuclide, $u(CF)$ is the fractional uncertainty estimate on the calibration setting for a specific geometry and radionuclide, $u(A_{repro})$ is the fractional uncertainty component for the reproducibility

of the system and $u(A_{linear})$ is the fractional linearity uncertainty (commonly provided by the manufacturer of the radionuclide calibrator, or can also be estimated by the user for the linearity range of the measurement).

4.2. Radionuclide calibrator measurements using a traceable calibration setting for a syringe

In this section, the process to fill a phantom (of an arbitrary size or shape) with a radioactive solution is described. The total activity in the phantom is calculated using a traceable calibration setting for a syringe and the syringe is used to transfer the solution to the phantom. The syringe and background (i.e., measurement without sources in or near the chamber) should be measuring using the same calibration setting. It is recommended to use the same clock and with an accuracy of at least 1 second.

Phantom preparation and radionuclide calibrator measurements

1. Fill a syringe with the radionuclide solution to be dispensed (same syringe brand, model, and volume used for determining calibration setting).
2. Measure the background (b_1) on the radionuclide calibrator.
3. Measure the full syringe (syringe full) in the radionuclide calibrator using the appropriate calibration setting and note the time of measurement (a_1, t_1).
4. Dispense activity to the phantom using the syringe.
5. After dispensing the solution, refill the syringe with carrier to the same volume as before dispensing to the phantom.
6. Measure the background (b_2) on the radionuclide calibrator.
7. Measure the syringe (residue syringe) in the radionuclide calibrator (a_2, t_2).
8. a_1 and a_2 should be corrected for the corresponding BG measurements (b_1 and b_2) and decay corrected to a common reference time (t_{ref}) using equation (4).
9. The total activity in the phantom can be calculated from the decay and background corrected activities (A_1 and A_2) using equation (8).

$$A_{\mathrm{ph}}(t_{\mathrm{ref}}) = \left(A_1(t_{\mathrm{ref}}) - A_2(t_{\mathrm{ref}})\right) \quad (8)$$

Uncertainty estimation

10. If the radionuclide calibrator output can be recorded as a current response, with the assumption that the half-life ($t_{1/2}$) of the radionuclide >> ($t_{ref} - t_1$) and $t_{1/2}$ >> ($t_1 - t_2$), and therefore the uncertainty associated with these components approximates to zero and also the correlation between these terms will also approximate to zero, the combined uncertainty for the total activity ($u(A_{total}(t_{ref})$) dispensed to the phantom can be estimated using equation (9).

$$u\left(A_{\mathrm{ph}}(t_{\mathrm{ref}})\right)^2 = \sum_{i=1}^{2}\left[\left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial a_{\mathrm{i}}}\right)^2 u\,(a_{\mathrm{i}})^2 + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial b_{\mathrm{i}}}\right)^2 u\,(b_{\mathrm{i}})^2 + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial t_{\mathrm{i}}}\right)^2 u\,(t_{\mathrm{i}})^2\right] + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial \lambda}\right)^2 u\,(\lambda)^2 + 2\,.\left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial A_1}\right)\left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial A_2}\right)u(A_1, A_2) \tag{9}$$

11. The measurements a_1, a_2, and the corresponding background measurements (b_i) are correlated when using the same calibration setting and radionuclide calibrator. Equation(10) is a simplification of equation (9) and considers the correlations.

$$u(A_{\mathrm{ph}}(t_{\mathrm{ref}}))^2 = \sum_{i=1}^{2}\left[\left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial a_{\mathrm{i}}}\right)^2 u\,(a_{\mathrm{i}})^2 + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial b_{\mathrm{i}}}\right)^2 u\,(b_{\mathrm{i}})^2 + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial t_{\mathrm{i}}}\right)^2 u\,(t_{\mathrm{i}})^2\right] + \left(\frac{\partial A_{\mathrm{ph}}(t_{\mathrm{ref}})}{\partial \lambda}\right)^2 u\,(\lambda)^2 + A_{\mathrm{ph}}(\mathrm{tref})^2 u\,(CF)^2 + A_{\mathrm{ph}}(\mathrm{tref})^2 u\,(A_{\mathrm{repro}})^2 + A_{\mathrm{ph}}(\mathrm{tref})^2 u\,(A_{\mathrm{linear}})^2 \tag{10}$$

Where, $u(a_i)$ and $u(b_i)$ correspond to the statistical uncertainty, $u(\lambda)$ is the uncertainty on the decay constant of the radionuclide, $u(CF)$ is the fractional uncertainty estimate on the calibration setting for a specific geometry and radionuclide, $u(A_{repro})$ is the fractional uncertainty component for the reproducibility of the system and $u(A_{linear})$ is the fractional linearity uncertainty (commonly provided by the manufacturer of the radionuclide calibrator, or can also be estimated by the user for the linearity range of the measurement).

4.3. Radionuclide calibrator measurements using a traceable calibration setting for a vial and calibrated balance

If a calibrated balance with enough capacity and resolution is available, the radionuclide solution can be dispensed to the phantom gravimetrically. This requires knowledge of the activity per unit mass of the stock solution, measurement of a container in a radionuclide calibrator and determining the total mass dispensed to the phantom. In Appendix 4, an example is presented for filling a cylindrical phantom using this method.

Radionuclide calibrator measurements

1. Select a measurement geometry (e.g., vial) for which the radionuclide calibrator has previously been calibrated against international standards. This will be the vial where the stock solution will be prepared.
2. Weigh vial empty (i.e., before receiving radioactive solution) (m_{empty}).
3. Dispense solution to the vial.
4. Weigh vial full (m_{full}).
5. Measure the background (b_1) on the radionuclide calibrator, i.e., without sources in or near the chamber using the same calibration setting as a_1.
6. Measure vial full in the radionuclide calibrator using an appropriate calibration setting and note the time of measurement (a_1, t_1).
7. a_1 should be corrected for the corresponding BG measurement (b_1) and decay corrected to a common reference time (t_{ref}) using equation (4).
8. Calculate the total mass dispensed to the vial,

$$\Delta m = m_{full} - m_{empty} \tag{11}$$

9. Calculate the activity per unit mass at the reference time ($A_m(t_{ref})$) of the stock solution using equation (12).

$$A_{\mathrm{m}}(t_{\mathrm{ref}}) = \frac{(A_1)}{(\Delta m)} \tag{12}$$

Uncertainty estimation – Activity per unit mas

10. The measurements a_1, and the corresponding background measurement (b_1) are correlated when using the same calibration setting and radionuclide calibrator. When considering the correlations, equation (13) can be used to estimate the combined uncertainty of $A_1(t_{ref})$.

$$\begin{aligned} u(A_1(t_{\text{ref}}))^2 = & \left(\frac{\partial A_1(t_{\text{ref}})}{\partial a_1}\right)^2 u\,(a_1)^2 + \left(\frac{\partial A_1(t_{\text{ref}})}{\partial b_1}\right)^2 u\,(b_1)^2 \\ & + \left(\frac{\partial A_1(t_{\text{ref}})}{\partial t_1}\right)^2 u\,(t_1)^2 \\ & + \left(\frac{\partial A_1(t_{\text{ref}})}{\partial \lambda}\right)^2 u\,(\lambda)^2\ A_1(t_{\text{ref}})^2 u\,(CF)^2 \\ & + A_1(t_{\text{ref}})^2 u\,(A_{\text{repro}})^2 + A_1(t_{\text{ref}})^2 u\,(A_{\text{linear}})^2 \end{aligned} \tag{13}$$

Where, $u(a_1)$ and $u(b_1)$ correspond to the statistical uncertainty, $u(\lambda)$ is the uncertainty on the decay constant of the radionuclide, $u(CF)$ is the fractional uncertainty estimate on the calibration setting for a specific geometry and radionuclide, $u(A_{repro})$ is the fractional uncertainty component for the reproducibility of the system and $u(A_{linear})$ is the fractional linearity uncertainty (commonly provided by the manufacturer of the radionuclide calibrator).

11. The standard uncertainty for the activity per unit mass ($u(A_m(t_{ref}))$ can be calculated using,

$$\left(\frac{u(A_m(t_{ref}))}{A_m(t_{ref})}\right)^2 = \left(\frac{u(A_1(t_{ref}))}{A_1(t_{ref})}\right)^2 + \left(\frac{u(\Delta m)}{\Delta m}\right)^2 \tag{14}$$

where $u(\Delta m)$ is the weighing uncertainty calculated using the accuracy of the balance assuming a rectangular probability distribution.

Phantom preparation

12. The stock solution can now be dispensed to the phantom. The mass dispensed to phantom ($\Delta m_{phantom}$) can be calculated by weighing the container (full and empty) used to dispense the solution to the phantom and/or by weighing the phantom (receiving container) empty and full. This depends on the available balance and its accuracy and readability and, the phantom size.

13. The total activity ($A_{ph}(t_{ref})$) dispensed to the phantom can be calculated using equation (15).

$$A_{ph}(t_{\mathrm{ref}}) = A_{\mathrm{m}}(t_{\mathrm{ref}}).\Delta m_{\mathrm{phantom}} \quad (15)$$

Uncertainty estimation

14. The standard combined uncertainty for the phantom activity can be calculated using,

$$\left(\frac{u(A_{ph}(t_{ref}))}{A_{ph}(t_{ref})}\right)^2 = \left(\frac{u(A_m(t_{\mathrm{ref}}))}{A_{\mathrm{m}}(t_{\mathrm{ref}})}\right)^2 + \left(\frac{u(\Delta m_{\mathrm{phantom}})}{\Delta m_{\mathrm{phantom}}}\right)^2 \quad (16)$$

The same methodology can be applied to calculate the activity per unit mass of a stock solution prepared in any geometry for which a traceable calibration setting is available (e.g., a syringe). Method 4.3 is reliable only if the activity per unit mass in the solution is homogeneous and no activity attaches to the vessel wall. This can be checked when measuring the residue vial or syringe or by means of transfer measurements. Alternatively, the phantom can be made from a stock solution and vials can be prepared and measured in the radionuclide calibrator to check the homogeneity of solution.

Chapter 5

Methods for the preparation of phantoms from a stock solution with an activity per unit mass traceable to national standards

To estimate the activity per unit mass in a phantom, it is necessary to know the total mass of solution dispensed to the phantom. Alternatively, if the nominal volume is known from the manufacturer, the activity concentration can be estimated with the caveat that a larger uncertainty would be associated due to the accuracy of the nominal volume provided by the manufacturer.

The preparation of a stock solution requires *a priori* knowledge of i) the total activity needed in the phantom, ii) the geometry for the radionuclide calibrator measurements, and iii) a balance with enough resolution, capacity and accuracy.

The preparation of stock solution would be a compromise between the amount of activity needed to dispense to the phantom but also the amount of activity and volume needed for the radionuclide calibrator measurement. Depending on the radionuclide of interest, the total activity needed for measurement will vary to ensure an accurate measurement of the activity.

5.1. Preparation of radioactive stock solution

1. Select a suitable container for the preparation of stock solution, hereafter stock solution bottle. Glass bottles are recommended if the solution is going to be stored.
2. Select a balance with an appropriate accuracy to weigh solution dispensed to the stock solution bottle. Take care that the balance has enough capacity to weigh the container empty and when full.
3. Weigh the stock solution bottle empty ($m_{stock\text{-}empty}$).
4. Dispense solution (this can be a combination of active and carrier solutions or just active solution depending on the required volume) to stock solution bottle. To avoid homogeneity problems, use an appropriate carrier solution – see Appendix 3 for carrier examples. Avoid using tap water as a carrier solution.
5. Weigh the stock solution bottle full ($m_{stock\text{-}full}$).
6. If both active and carrier solutions are used, mix the solution in the stock solution bottle. Always mix the solution in the stock solution bottle before dispensing to additional containers.
7. Calculate total mass dispensed to the stock solution bottle ($\Delta m_{stock} = m_{stock\text{-}full} - m_{stock\text{-}empty}$).

5.2. Measurement of activity per unit mass of stock solution

1. From the stock solution prepared in 5.1, dispense a radioactive source suitable to be measured to estimate activity per unit mass in the source and stock solution.

   Note 1: This source should match the geometry used for the calibration of the radionuclide calibrator.

   Note 2: To check homogeneity of solution, two sources can be prepared, one before dispensing to the phantom and one after.

2. Weigh the receiving container empty ($m_{RC\text{-}empty}$).
3. Using a syringe (or an alternative dispensing container) dispense solution from stock solution bottle to measurement container.
4. Weigh the receiving container full ($m_{RC\text{-}full}$).
5. Calculate total active mass dispensed to the container ($\Delta m_{RC} = m_{RC\text{-}full} - m_{RC\text{-}empty}$).

   Note 3: Stock solution should have enough volume, such that the volume in the measurement container matches that used for the calibration of the radionuclide calibrator.

6. Measure the background (b_1) on the radionuclide calibrator, i.e., without sources in or near the chamber. The background measurement should be performed with the same calibration setting as the container (syringe or vial).
7. Measure the container in the radionuclide calibrator and note the time of measurement (a_1, t_1).
8. a_1 should be corrected for the corresponding background measurement (b_1) and decay corrected to a reference time (t_{ref}) (optional) using equation (4).
9. Calculate the activity per unit mass of stock solution using equation (17).

$$A_{\mathrm{m}}(t_{\mathrm{ref}}) = \frac{(A_1)}{\Delta m_{\mathrm{RC}}} \tag{17}$$

10. Repeat steps 2 to 10 to make additional containers to be measured on the radionuclide calibrator.
11. If more than one container is made, activities must be background and decay corrected to a common reference time (t_{ref}) (optional) using equation (4).

Uncertainty estimation

12. The measurements a_1, and the corresponding background measurement (b_1) are correlated when using the same calibration setting and radionuclide calibrator. When considering the correlations, equation(7) can be used to estimate the uncertainty of $A_1(t_{ref})$.

$$u(A_1(t_{\text{ref}}))^2 = \left(\frac{\partial A_1(t_{\text{ref}})}{\partial a_1}\right)^2 u\,(a_1)^2 + \left(\frac{\partial A_1(t_{\text{ref}})}{\partial b_1}\right)^2 u\,(b_1)^2 + \left(\frac{\partial A_1(t_{\text{ref}})}{\partial t_1}\right)^2 u\,(t_1)^2 + \left(\frac{\partial A_1(t_{\text{ref}})}{\partial \lambda}\right)^2 u\,(\lambda)^2\ A_1(t_{\text{ref}})^2 u\,(CF)^2 + A_1(t_{\text{ref}})^2 u\,(A_{\text{repro}})^2 + A_1(t_{\text{ref}})^2 u\,(A_{\text{linear}})^2 \quad (18)$$

Where, $u(a_1)$ and $u(b_1)$ correspond to the statistical uncertainty, $u(\lambda)$ is the uncertainty on the decay constant of the radionuclide, $u(CF)$ is the fractional uncertainty estimate on the calibration setting for a specific geometry and radionuclide, $u(A_{repro})$ is the fractional uncertainty component for the reproducibility of the system and $u(A_{linear})$ is the fractional linearity uncertainty (commonly provided by the manufacturer of the radionuclide calibrator).

13. The standard uncertainty for the activity per unit mass, $u(A_m(t_{ref}))$, can be calculated using,

$$\left(\frac{u(A_m(t_{ref}))}{A_m(t_{ref})}\right)^2 = \left(\frac{u(A_1(t_{ref}))}{A_1(t_{ref})}\right)^2 + \left(\frac{u(\Delta m_{RC})}{\Delta m_{RC}}\right)^2 \quad (19)$$

where $u(\Delta m_{RC})$ is the weighing uncertainty calculated using the accuracy of the balance assuming a rectangular probability distribution.

5.3. Preparation of phantom using the radioactive stock solution

1. Select an appropriate accuracy balance to weigh the phantom. Depending on the size of the phantom this might be different from the balance used to prepare the stock solution.
2. Weigh the phantom empty ($m_{phantom\text{-}empty}$).
3. Depending on the volume of the phantom, additional carrier solution can be used to make the total volume of the phantom.

   Note 1: If additional carrier solution is used, carrier solution should be added to the phantom before dispensing the active solution (from stock solution bottle). This is more significant when large phantoms are used. This is to avoid evaporation of the radioactive solution when dispensing to large volumes.

   Note 2: When adding additional carrier to the phantom ensure that there is enough volume left for filling the phantom with active solution and that enough space is left to mix the solution in the phantom. A general rule of thumb it is to fill the phantom to 3/4 of its capacity with carrier, add active solution and mix the solution in the phantom. After filling the phantom with the active solution, fill the remaining of the phantom with carrier solution and mix.
4. Using a syringe (or an alternative dispensing container) remove solution from stock solution bottle.
5. Weigh the dispensing container full using an appropriate balance (m_{full}).
6. Dispense the solution to the phantom.
7. Mix the solution in the phantom to ensure a homogeneous solution.
8. Weigh the dispensing container after dispensing solution to phantom ($m_{residue}$).
9. Fill the remaining of the phantom with carrier (if necessary).
10. Weigh the phantom full ($m_{phantom\text{-}full}$).
11. Calculate total mass dispensed to the phantom ($\Delta m_{total\text{-}phantom} = m_{phantom\text{-}full} - m_{phantom\ empty}$).
12. Calculate total active mass dispensed to the phantom ($Am_{active\text{-}phantom} = m_{full} - m_{residue}$).
13. Calculate total activity in the phantom at reference time using equation (20).

$$A_{\text{ph}}(t_{\text{ref}}) = A_{\text{m}}(t_{\text{ref}}).\,\Delta\text{m}_{\text{active-phantom}} \quad (20)$$

Uncertainty estimation

14. Estimate the uncertainty on the total activity at a reference time in the phantom using equation (21).

$$\left(\frac{u(A_{ph}(t_{ref}))}{A_{ph}(t_{ref})}\right)^2 = \left(\frac{u(A_{\text{m}}(t_{\text{ref}}))}{A_{\text{m}}(t_{\text{ref}})}\right)^2 + \left(\frac{u(\Delta\text{m}_{\text{active-phantom}})}{\Delta m_{\text{active-phantom}}}\right)^2 \quad (21)$$

15. If different from stock solution (i.e., when additional carrier added to phantom), estimate activity per unit mass in the phantom using equation (22).

$$A_m^{phantom}(t_{\text{ref}}) = \frac{A_{\text{ph}}(t_{\text{ref}})}{\Delta\text{m}_{\text{total-phantom}}} \quad (22)$$

16. Estimate the uncertainty on the activity per unit mass in the phantom using equation (23).

$$\left(\frac{u(A_m^{phantom}(t_{ref}))}{(A_m^{phantom}(t_{ref})}\right)^2 = \left(\frac{u\left(A_m^{phantom}(t_{ref})\right)}{A_m^{phantom}(t_{ref})}\right)^2 + \left(\frac{u(\Delta\text{m}_{\text{total-phantom}})}{\Delta\text{m}_{\text{total-phantom}}}\right)^2 \quad (23)$$

Chapter 6

Final remarks

This good practice guide has been developed based on the authors' combined experiences in preparing radioactive phantoms in both hospital settings and at the National Physical Laboratory. Its primary goal is to provide a range of reproducible methods for preparing a phantom that can be performed with the most common clinical and laboratory based experimental setups.

The methods described in this work will result in a traceable measurement of the activity dispensed to a phantom. However, when performing routine measurements, it should be remembered that measurement traceability is a property of an individual measurement, not the equipment used to make the measurement. As such, failure to follow the procedures set out in this document (or an appropriate modification of them) when making a measurement will result in a measured value that cannot be fully traced back to an activity standard.

The adaption of the guidance in this document into site specific standard operating producers and reporting templates can be a critical practical step in ensuring traceability for all measurements.

Chapter 7

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Appendix 1

Suggested carrier solutions

In Table 1, suggested carrier solutions are given for commonly used radionuclides in nuclear medicine. Alternative carrier solutions can be used, assuming the solution is chemically stable. The carrier solution is important to ensure that the radioactive component stays in solution and therefore, not attached to the walls of phantoms/dispensing vessels.

Table 1: *Suggested carrier solutions for commonly used radionuclides in Nuclear Medicine. These are not prescriptive and different suitable concentrations can be used. Refer to* (35) *for more details on the preparation of carriers.*

Radionuclide	Suggested Carrier solution
^{90}Y	Yttrium chloride in an aqueous solution of 0.1 mol L^{-1} hydrochloric acid also containing 1-10 µg g^{-1} of inactive yttrium.
^{99m}Tc	Sodium pertechnetate in an aqueous solution of 0.1 mol L^{-1} sodium hydroxide also containing 1-10 µg g^{-1} of inactive rhenium.
^{131}I	Sodium Iodide in an aqueous solution of 0.1 mol L^{-1} sodium hydroxide also containing 1-10 µg g^{-1} of inactive iodine.
^{177}Lu	Lutetium chloride in an aqueous solution of 0.1 mol L^{-1} hydrochloric acid also containing 1-10 µg g^{-1} of inactive lutetium.

Appendix 2

Example of preparation of carrier solution for ^{177}Lu

The following example demonstrates the preparation of 2 litres of lutetium chloride as 0.1 mol L^{-1} HCl also containing 10 µg g^{-1} of inactive lutetium. The process described below is an example and the methods described are not prescriptive.

Equipment

Equipment	Notes
Containers	Appropriate bottles should be available. These can be plastic or glass.
De-ionised water	Tap water shall not be used for the preparation of carrier solutions.
Concentrated Hydrochloric Acid	In this example, 1 mol L^{-1} HCl. Other concentrations can be used.
Balance	Volumetric glassware can also be used if dispensing large amounts.
Inactive standard element	In this example, a lutetium standard at a concentration of 1000 µg g^{-1} will be used. Other concentrations are available.

Method

1. Calculate the total amount of inactive lutetium standard (*total inactive element*) needed to achieve the expected concentration of 10 µg g^{-1} in a total volume of 2 L of solution.

$$total\ inactive\ element = expected\ concentration \times total\ volume \quad (24)$$

Therefore, in this example:

$$total\ inactive\ element = 10\ \mu g\ g^{-1} \times 2000\ g = 20\ 000\ \mu g$$

2. In this example, the concentration of the inactive standard is 1000 µg g^{-1} and therefore the total amount of this standard to be dispensed to the bottle shall be calculated.

$$Amount\ of\ inactive\ standard = \frac{total\ inactive\ element}{concentration\ of\ standard} \quad (25)$$

Therefore, in this example:

$$Amount\ of\ inactive\ standard = \frac{20000\ \mu g}{1000\ \mu g\ g^{-1}} = 20\ g$$

3. Calculate the amount of hydrochloric acid (molarity of 1 mol L^{-1}) to be dispensed to the bottle to achieve 0.1 mol L^{-1} HCl in 2 L of solution. In equation (26), *M1* corresponds to the concentration (in Molar) of the initial solution, *V1* corresponds to the volume of initial solution, *M2* is the concentration of the diluted solution (in Molar) and *V2* is the volume of the diluted solution.

$$M1.V1 = M2.V2 \quad (26)$$

In this example, *M1*, *M2* and *V2* are known.

$$V1 = \frac{M2.V2}{M1} \quad (27)$$

Therefore:

$$V1 = \frac{0.1\ mol\ L^{-1} \times 2000\ mL}{1\ mol\ L^{-1}} = 200\ mL$$

4. Correct *V1* for the density of 1 mol L^{-1}.

$$V1_{corr.} = \frac{200}{1.010} = 198\ mL$$

5. Calculate the volume of de-ionised water ($V_{d\text{-}water}$) to achieve a total volume (V_{total}) of 2L of solution in the bottle.

$$V_{\text{d-water}} = V_{\text{total}} - (Amount\ of\ inactive\ standard + V1_{\text{corr.}}) \quad (28)$$

In this example:

$$V_{\text{d-water}} = 2000 - (20 + 198) = 1782\ mL$$

6. Find appropriate container for the preparation of the carrier.
7. Label container with the appropriate name and respective chemical hazard symbol(s).
8. Dispense de-ionised water, in this example 1782 mL, this can be done gravimetrically or using a volumetric container.
9. Dispense 198 mL of the hydrochloric acid gravimetrically or volumetrically.
10. Dispense 20 g (or 20 mL) of the lutetium inactive standard.
11. Mix the solution in the container.

Appendix 3

Example of filling a phantom and estimation of uncertainties – calibration setting for vial & no balance available

In the following example, the process described in section 4.1 is followed to fill a cylindrical Jaszczak phantom with 400 MBq of ^{177}Lu (n.c.a) as lutetium chloride. In this example, a balance is not available for weighing any of the containers and therefore the total activity is estimated using the radionuclide calibrator measurements of the vial and the syringe used to dispense the solution from the vial to the phantom.

Preparation of carrier solution

The carrier solution was prepared following the process described in Appendix 2. To prepare the cylindrical Jaszczak phantom and the vial, approximately 7 L of lutetium chloride carrier solution were prepared. The carrier solution used for diluting the solution in the phantom was lutetium chloride containing 1 μg g^{-1} of inactive lutetium in 0.1 mol L^{-1} HCl.

For the carrier solution, a lutetium standard solution at a concentration of 1000 μg mL^{-1}, 1 mol L^{-1} HCl and de-ionised water were used. The solution was made in a gravimetric 10 L bottle, the inactive standard and HCl were weighted before dispensing to the large bottle. The solution was mixed in the bottle at the time of preparation, and before use each use.

The water was dispended first, followed by the concentrated acid and the inactive element, therefore, before start making the solution the amount of concentrated HCl, inactive element and de-ionised water were calculated.

- Inactive lutetium standard: to obtain 1 μg g^{-1} in the total volume of 7 L, using the standard solution at a concentration of 1000 μg g^{-1}, a total amount of 7 g of inactive element was used.
- Concentrated acid: a total volume of 693 mL of 1 mol L^{-1} HCl was used to achieve 0.1 mol L^{-1} HCl concentration assuming a total volume of 7 L of the final solution.
- De-ionised water: the total volume of carrier solution needed to make the phantom was approximately 7 L therefore, approximately 6300 mL of de-ionised water was needed.

Cylindrical Jaszczak phantom preparation

Before adding the radioactive solution to the phantom, the phantom was filled with the previously prepared carrier, to 2/3 of its capacity.

Approximately 0.1 g of ^{177}Lu solution was received from the supplier in a glass vial. The solution was diluted in the supplier vial using the carrier solution previously prepared before transferring the solution to another container.

A 10R Schott vial was filled with ~ 4 mL of radioactive solution with a total activity of approximately 435 MBq of ^{177}Lu as lutetium chloride. A unique identifier was given to this vial – vial-01. The vial was measured in the radionuclide calibrator, details of the activity

measurements are presented in the next section and a summary of the measurements can be seen in Table 2.

The solution in vial-01 was dispensed to the cylindrical Jaszczak phantom using a syringe labelled with a unique identifier syringe-01. Before dispensing the solution to the phantom, syringe-01 containing the radioactive solution was measured on the radionuclide calibrator and the measurement results are reported in Table 4. After dispensing to the phantom, vial-01 and syringe-01 were then filled with ~ 4 mL of carrier solution to match the initial volume of solution and called vial-01 + carrier and syringe-01 + carrier respectively. The containers were then measured on the radionuclide calibrator in the same positions and calibration setting as vial-01 and syringe-01 and the respective measurement results are reported in Table 4.

After the radioactive solution was dispensed to the cylindrical Jaszczak, the solution in the phantom was mixed and the remaining of the phantom was filled with carrier, care was taken to avoid air bubbles in the phantom. Before mixing the solution, the phantom was sealed.

Radionuclide calibrator measurements

In this example, the radionuclide calibrator used for the activity measurements was previously calibrated against primary standards for 4 mL of solution in a 10R Schott vial and placed in a standard position in the dedicated holder. The radionuclide calibrator used was maintained and a robust QC and QA programmes were in place.

Before starting the measurements on the radionuclide calibrator, the calibration setting on the radionuclide calibrator was set to match that previously derived for a 4 mL of ^{177}Lu in a 10R Schott vial. 10 background (BG) readings were taken before each measurement, and the average value and respective standard deviation (SD) were calculated. Vial-1 was then placed in the radionuclide calibrator using the dedicated source holder, 10 readings were taken, and the respective time of measurement was noted down. The BG and vial-01 measurements were performed using the same calibration setting. The measurements for vial-01 were corrected for the average background and decay corrected to a common reference time 27/02/2023 at 14:00:00 UTC. The standard deviation was calculated. In Table 2 a summary of the radionuclide calibrator measurements is presented.

Table 2: *Radionuclide calibrator measurements of vial-01. The measurement results are corrected for background (BG) and decay corrected to a common reference time 27/02/2023 14:00:00 UTC. The mean value and respective standard deviation were also calculated.*

Reading Number	Activity (MBq)	Activity corrected for BG (MBq)	Time of measurement (UTC)	Activity decay corrected to reference time (MBq)
1	438.0	437.9	27/02/2023 13:10:10	436.3
2	438.0	437.9	27/02/2023 13:10:20	436.3
3	436.9	436.8	27/02/2023 13:10:30	435.2
4	438.0	437.9	27/02/2023 13:10:40	436.3
5	436.9	436.8	27/02/2023 13:10:50	435.2
6	436.9	436.8	27/02/2023 13:11:00	435.3
7	438.0	437.9	27/02/2023 13:11:10	436.3
8	438.0	437.9	27/02/2023 13:11:20	436.3
9	438.0	437.9	27/02/2023 13:11:30	436.4
10	436.9	436.8	27/02/2023 13:11:40	435.3
			Mean Value	435.9 MBq
			SD (%)	0.13
			Reference Time (UTC)	27/02/2023 14:00:00

An uncertainty budget for the measurement of the full vial ($A_{initial}$) is presented in Table 3. In the example, a simplified version of the LPU was used as described in section 4.1.17 to 4.1.18 of this document.

The main sources of uncertainty were identified and are described in Table 3. For each source of uncertainty, an uncertainty value has been estimated and reported in the table. For the calibration setting, reproducibility and linearity, the uncertainty values have been estimated *a priori* since these are associated with the performance of the radionuclide calibrator. The probability distribution for these components have been defined as normal distribution, and therefore the divisor has been set to 1. The standard uncertainty ($u(x_i)$) therefore is the same

value as the uncertainty value, since it corresponds to the uncertainty value divided by the divisor. The sensitivity coefficients (c_i) are also presented in the table.

In this example there were no impurities present in the solution and the volume used for the radionuclide calibrator measurements matched the calibration geometry. The uncertainty on the calibration setting was estimated at the time of the calibration against international standards.

Table 3: *Uncertainty budget for the activity of the initial vial (A_1) measured on a radionuclide calibrator. The combined uncertainty is reported. The expanded uncertainty is not reported in the table.*

Component	Uncertainty value	Probability Distribution	Divisor	$u(x_i)$	c_i	u_i (A_1)
Calibration setting	4.4	normal	1	4.4	1	19.0
Reproducibility	2.2	normal	1	2.2	1	4.8
Linearity	4.4	normal	1	4.4	1	19.0
Activity (a_1)	0.013	normal	1	0.013	1	1.6×10^{-6}
Background (b_1)	0.032	normal	1	0.032	-1	0.0010
Decay correction	1.2×10^{-5}	normal	1	1×10^{-5}	-1.5	3.4×10^{-10}
t_1	0.017	rectangular	$\sqrt{3}$	0.010	4.6	0.0020
t_{ref}	0.017	rectangular	$\sqrt{3}$	0.010	-4.6	0.0019
			Combined uncertainty (u_c)			6.5
			u_c (%)			1.5

Vial-01+carrier measurements (A_4)

After the solution was removed using a syringe, 4 mL of carrier solution (to match the initial volume) was added to vial-01. The vial was then measured on the radionuclide calibrator in the same conditions and calibration setting as vial-01. The measurements were corrected for BG and decay corrected to the common reference time. The mean value corrected for BG and decay corrected and respective standard deviation are reported in Table 4.

Table 4: *Summary of the radionuclide calibrator measurements for vial-01, vial-01+carrier, syringe-01 and syringe-01+carrier. The mean values reported are corrected for background and decay corrected to a common reference time. The standard deviations are also reported in percentage.*

	vial-01 (A_1)	**vial-01 + carrier (A_4)**	**syringe-01 (A_2)**	**syringe-01 + carrier (A_3)**
Mean value (MBq)	435.9	11.4	445.2	10.3
Standard deviation	0.13	0.14	0.19	0.46
Reference Time (UTC)	27/02/2023 14:00:00	27/02/2023 14:00:00	27/02/2023 14:00:00	27/02/2023 14:00:00

Syringe-01 measurements (A_{full}) & syringe-01+carrier measurements (A_{empty})

Syringe-01 and syringe-01+carrier were measured on the radionuclide calibrator using a common calibration setting. The syringe was placed in the 'syringe hole' of the dedicated holder. The measurements were corrected for background and decay corrected and the mean value and respective standard deviations are reported in Table 4.

Total activity in the phantom and respective uncertainty

The total activity in the phantom was calculated using equation (14) and the respective uncertainty was estimated using the LPU and assumptions were made to match this measurement model as described in section 4.1.17 to 4.1.18.

In the table below, an uncertainty budget is presented for the uncertainty associated with the total activity in the phantom.

Table 5: *Uncertainty budget for total activity in the phantom at the reference time (standard uncertainties at k=1). Probability distribution, divisors and sensitivity coefficients excluded from the table.*

Component	**Uncertainty ($A_{ph}t_{ref}$))**
Calibration setting	17.2
Reproducibility	4.3
Linearity	17.2
Activity (a_1)	1.6×10^{-6}
Activity (a_2)	1.9×10^{-6}
Activity (a_3)	6.3×10^{-18}
Activity (a_4)	1.3×10^{-8}
Background (b_1)	0.0010
Background (b_2)	0.00091
Background (b_3)	1.8×10^{-15}
Background (b_4)	6.2×10^{-7}
Decay correction	1.5×10^{-8}
t_1	0.0019
t_2	1.2×10^{-6}
t_3	6.5×10^{-10}
t_4	3.3×10^{-13}
t_{ref}	0.0011
Combined uncertainty (u_c)	6.2
u_c (%)	1.5

The total activity calculated in the phantom was 414.7 (62) MBq at a reference time 27/02/2023 at 14:00 UTC. The combined standard uncertainty (in percentage and absolute value) corresponds to the uncertainty on the total activity dispensed to the phantom. The input sources of uncertainty have a normal distribution and therefore it is acceptable to assume the uncertainty of the total activity ($A_{total}(t_{ref})$) also has a normal distribution. Therefore, to calculate the expanded uncertainty (U), a coverage factor of 2 (k = 2) can be used, and this gives an expanded uncertainty of 12.4 MBq, and therefore the total activity can be reported as 415 (13) MBq.

Appendix 4

Example of filling a phantom and estimation of uncertainties – calibration setting for vial & balance available

In this example, the solution is dispensed to the phantom gravimetrically, the radioactive solution is measured using a radionuclide calibrator previously calibrated for the geometry and radionuclide being measured, and the activity per unit mass is calculated. The methods presented in section 5 were followed. The radionuclide calibrator used in this example for the measurements is calibrated for 4 mL of solution in a 10R Schott vial.

Preparation of carrier solution

See Appendix 2 for an example on the preparation of 0.1 mol L^{-1} HCl also containing 1 μg g^{-1} of inactive lutetium.

Preparation of cylindrical Jaszczak phantom using stock solution

The radioactive solution was dispensed to the Cylindrical Jaszczak phantom gravimetrically. In this example, the balance used had a resolution of 0.001 g and a capacity of 100 g.

Before dispensing the radioactive solution to the phantom, the phantom was filled with carrier solution up to 2/3 of its capacity.

In this example, a radioactive stock solution containing approximately 600 MBq in approximately 24 mL of ^{177}Lu as lutetium chloride in 0.1 mol L^{-1} HCl with 1 μg g^{-1} of inactive lutetium was prepared. From the stock solution, 4 mL were dispensed gravimetrically to two 10R Schott vials. The vials were weighed before and after dispensing the solution and measured on the radionuclide calibrator. The two 10R Schott vials were assigned unique identifiers, vial-02 and vial-03. The remaining solution (~ 16 mL) was dispensed gravimetrically to the cylindrical phantom, the syringe was weighed empty and full. Vial-02 was prepared before dispensing the solution to the phantom, and vial-03 was dispensed after the solution was dispensed to the phantom. This was to check, that the stock solution was homogeneous.

Radionuclide calibrator measurements

The activity in vial-02 and vial-03 were measured in the radionuclide calibrator has previously described in Appendix 3. The measurements of vial-02 and vial-03 were in statistical agreement, and the results of vial-02 were used for further calculations. The total activity and activity per unit mass in vial-02 and respective uncertainty are reported in Table 6 along with the total activity dispensed to the phantom. For an example on an uncertainty budget for an activity measurement on a radionuclide calibrator see Table 3. The combined standard uncertainty was calculated using the law propagation of uncertainty (LPU), a rectangular probability distribution was assumed for the weighing. Sensitivity factors of 1 were assigned to the uncertainty in the activity in the vial and the uncertainty in the mass dispensed to the vial.

Table 6: *Total activity in vial-02 measured on the radionuclide calibrator and respective uncertainty. Total active mass and activity per unit mass in vial-02 is also presented in the table. The uncertainties reported are standard combined uncertainties, the coverage factor k=1.*

Stock Solution	
Active mass in 10R Schott vial (vial-02)	4.0170 g
Activity in vial-02	100.4 (15) MBq
Measurement time	27/02/2023 9:00:00 UTC
Activity per unit mass stock solution	24.99 (38) MBq g^{-1}
Mass dispensed to phantom	15.989 g

Total activity in the phantom and respective uncertainty

The activity in the phantom is calculated using the activity per unit mass of the initial solution and the total active mass dispensed to the phantom (equation (20)). The total calculated activity in the phantom is 399.6 (61) MBq on the 27 February 2023 at 9:00 (UTC), the reported uncertainty is a standard combined uncertainty. The expanded uncertainty can be estimated using the coverage factor of k=2 assuming a normal distribution.

An example of the uncertainty budget for the total activity in the cylindrical phantom is presented in Table 6.

Table 7: *Uncertainty budget for the total activity dispensed to the cylindrical Jaszczak phantom. Details on the uncertainty components for the radionuclide calibrator measurement are not presented in the table – these were discussed in Appendix 3.*

Component	**Uncertainty (%) ($A_{ph}t_{ref}$)**
Activity per unit mass	1.5
Weighing (phantom)	0.011
Combined uncertainty (u_c)	1.50