

TECHNICAL REPORTS SERIES NO. 454

Quality Assurance for Radioactivity Measurement in Nuclear Medicine



IAEA

International Atomic Energy Agency

QUALITY ASSURANCE FOR
RADIOACTIVITY MEASUREMENT
IN NUCLEAR MEDICINE

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INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2006

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tel.: +43 1 2600 22417
email: sales.publications@iaea.org
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Printed by the IAEA in Austria
November 2006
STI/DOC/010/454

IAEA Library Cataloguing in Publication Data

Quality assurance for radioactivity measurement in nuclear medicine. —
Vienna : International Atomic Energy Agency, 2006.
p. ; 24 cm. — (Technical reports series, ISSN 0074-1914 ; no. 454)
STI/DOC/010/454
ISBN 92-0-105306-1
Includes bibliographical references.

1. Nuclear medicine — Quality control. 2. Radioactivity —
Measurement — Quality control. I. International Atomic Energy
Agency. II. Technical reports series (International Atomic Energy
Agency) ; 454.

IAEAL

06-00465

FOREWORD

The field of nuclear medicine continues to grow around the world, owing in part to a number of successful programmes carried out by the IAEA to enhance the use of nuclear medicine techniques in Member States. The implementation of quality assurance (QA) programmes to ensure the safe application of radiopharmaceuticals has, however, been variable in many Member States. One possible reason is the lack of a unified set of principles regarding the establishment of such programmes. This publication addresses the issue of QA programmes for radioactivity measurement in nuclear medicine.

A group of experts consulted by the IAEA recommended in 2002 that unified principles concerning QA and quality control (QC) procedures for the measurement of radioactivity in nuclear medicine be developed because of its importance in controlling the safety and effectiveness of the use of radiopharmaceuticals. This publication is the result of advice provided to the IAEA by experts in the fields of radionuclide metrology, medical physics and radiopharmacy.

This report can be considered to be a more detailed and updated version of IAEA-TECDOC-602, *Quality Control of Nuclear Medicine Instruments*, published in 1991. Advances in the field of nuclear instrumentation since that report was published, particularly in imaging, and the increased emphasis on QA and QC prompted the need for an update. Moreover, it was realized that the activity measurement and imaging aspects had each become so specialized as to be better treated in separate publications. The present report focuses on the factors affecting radioactivity measurement and the implementation of QA and QC programmes to ensure accurate and consistent results.

The IAEA has developed a safety standard on *The Management System for Facilities and Activities* (IAEA Safety Standards Series No. GS-R-3), which replaces the IAEA publications on QA issued as Safety Series No. 50-C/SG-Q (1996). In GS-R-3, the management system is described as a set of interrelated or interacting elements for establishing policies and objectives and enabling the objectives to be achieved in a safe and efficient way. The management system is designed to fulfil requirements that integrate elements related to safety, health, the environment, security, quality and economics. Safety is the fundamental principle upon which the management system is based.

It is also recognized in GS-R-3 that QC and QA are important components of the management system. While QC is a means of applying controls to ensure that the product or service consistently meets specifications, QA is an interdisciplinary management tool that provides a means for ensuring that all work is adequately planned, correctly performed and assessed.

A QA programme is designed primarily to ensure the quality of a product for a customer and may be appropriate to control the activities in radioactivity measurement in nuclear medicine. However, it would be more effective if these QA controls were integrated into a single management system.

There are numerous processes that review and assess financial and technical performance, the achievement of goals and the effectiveness of an organization's processes. It is necessary to integrate the results of all assessment activities to focus decision making on the needs of the business strategy. It is important to understand how assessments enable managers to achieve higher standards of performance.

The principles in this publication are based on those described in IAEA Safety Standards Series No. GS-R-3 and in the General Requirements for the Competence of Testing and Calibration Laboratories (ISO/IEC 17025:1999), which set requirements that testing and calibration laboratories must meet to demonstrate that they have a management system in place and are technically competent. The present report provides information specific to implementing these standards at both the end user (clinic) and the secondary standards radioactivity laboratory levels. If adopted to their greatest extent, the principles herein will provide the user with all the information (including measurement procedures) necessary to carry out most tasks associated with routine radioactivity measurement, including maintaining the necessary documentation.

The primary audience for this report includes radiopharmacists, nuclear medicine technologists, medical physicists, technicians in secondary standards radioactivity laboratories and managers responsible for the operation of such facilities.

The efforts of the following experts in drafting this publication are greatly appreciated: C. Herbst (South Africa), J. Norenberg (United States of America) and M. Woods (United Kingdom). The IAEA is also grateful to all of the contributors and reviewers who made very helpful suggestions.

The IAEA officer responsible for the preparation of this publication was B.E. Zimmerman of the Division of Human Health.

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CONTENTS

1.	INTRODUCTION	1
1.1.	Background	1
1.2.	Objective	2
1.3.	Scope	3
2.	NORMATIVE REFERENCES	3
3.	TERMS AND DEFINITIONS	4
4.	MANAGEMENT SYSTEM REQUIREMENTS	4
4.1.	Organization	4
4.2.	Quality assurance programme	6
4.3.	Document control	7
4.4.	Review of requests, tenders and contracts	8
4.4.1.	Providers of calibrated radioactive sources	8
4.4.2.	End users of radiopharmaceuticals and radioactive devices	9
4.5.	Subcontracting of tests and calibrations	10
4.6.	Purchase of services and supplies	10
4.6.1.	Equipment and services	11
4.6.2.	Radioactive sources	11
4.7.	Service to the client	12
4.8.	Complaints	12
4.9.	Control of non-conforming tests	12
4.10.	Corrective action	13
4.11.	Preventive action	13
4.12.	Control of records	14
4.13.	Internal assessments	14
4.14.	Management system reviews	15
5.	TECHNICAL REQUIREMENTS	16
5.1.	General	16
5.2.	Personnel	16
5.3.	Accommodation and environmental conditions	18
5.4.	Test and calibration methods and method validation	19

5.4.1.	General	19
5.4.2.	Quality control of radiopharmaceuticals	19
	5.4.2.1. Radionuclidic purity	21
	5.4.2.2. Radiochemical purity	21
	5.4.2.3. Chemical purity	22
	5.4.2.4. Chemical and radiochemical purity: Standards and procedures	22
	5.4.2.5. Pharmaceutical aspects	23
	5.4.2.6. Documentation	23
5.4.3.	Quality control of standardized calibration sources ...	24
	5.4.3.1. Chemical stability	24
	5.4.3.2. Radionuclidic purity	24
5.4.4.	Equipment calibration	25
5.4.5.	Method validation	26
5.4.6.	Estimation of uncertainty in measurement	26
5.5.	Equipment	27
	5.5.1. Specifications	27
	5.5.2. Maintenance	27
	5.5.3. Operation	28
5.6.	Measurement traceability	29
5.7.	Sampling	30
5.8.	Handling of test, measurement and calibration items	30
5.9.	Ensuring the quality of test and calibration items	31
5.10.	Reporting the results	32

APPENDIX I:	SAMPLE AUDIT OF QUALITY ASSURANCE FOR NUCLEAR MEDICINE RADIOACTIVITY MEASUREMENTS	33
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APPENDIX II:	SAMPLE DOCUMENTATION OF REQUIRED TRAINING AND EXPERIENCE	42
--------------	---	----

APPENDIX III:	RADIONUCLIDIC PURITY	48
---------------	----------------------------	----

APPENDIX IV:	CHEMICAL PURITY – SAMPLE PROCEDURE FOR ALUMINA BREAKTHROUGH TESTING...	54
--------------	---	----

APPENDIX V:	RADIOCHEMICAL PURITY TESTING OF ^{99m} Tc RADIOPHARMACEUTICALS	56
-------------	---	----

APPENDIX VI:	PARTICLE SIZE ESTIMATION OF ^{99m} Tc-MAA..	61
--------------	---	----

APPENDIX VII: MEASUREMENT OF RADIOACTIVITY	63
APPENDIX VIII: MEASUREMENT TRACEABILITY IN PRACTICE	76
REFERENCES	79
CONTRIBUTORS TO DRAFTING AND REVIEW	81

1. INTRODUCTION

1.1. BACKGROUND

The safe, efficient and efficacious practice of nuclear medicine involves the integration of a number of processes. The quality of each process will have an impact on the overall quality of the clinical procedure and the benefit imparted to the patient. It is important, therefore, that each process be conducted within the framework of a quality assurance (QA) programme that, if followed, can be shown to achieve the desired objectives with the desired accuracy.

The levels of activity in radiopharmaceuticals to be administered clinically are governed primarily by the need to balance the effectiveness and the safety of the medical procedure by choosing the minimum radiation dose delivered to the patient (hereinafter referred to simply as 'dose') needed to achieve the required objective (e.g. diagnostic image quality or therapeutic outcome). To realize this goal, it is important to keep in mind that a nuclear medicine procedure consists of several components, all of which must be controlled in order to have an optimal outcome. One example is renal screening using diuretics. If any one of the pharmaceuticals (diuretic, imaging agent, etc.) is not administered correctly, the entire procedure may need to be repeated. Assuming that those parts of the procedure not involving radioactivity are under control, the dose that is received by the patient from a radiopharmaceutical can be thought of as being controlled by a combination of the administered radioactivity and its chemical form.¹ The correctness of these factors is a primary determinant of the safe and efficacious use of these drugs.

The International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources (BSS) [1] and IAEA Safety Standards Series Nos GS-R-3 and GS-G-3.1 on the management system for facilities and activities [2, 3], together with the international standard for General Requirements for the Competence of Testing and Calibration Laboratories (ISO/IEC 17025) [4], require a QA programme as an integral part of the management system to control the practices and interventions in the use of all ionizing radiation for all applications. The preparation and administration of

¹ There are, of course, a larger number of variables that influence the actual dose received by the patient and by the individual organs (and tumour) themselves. These tend to be mostly biological in nature and are often unpredictable a priori. Discussion of such variables is beyond the scope of this report.

radiopharmaceuticals, whether for diagnostic or for therapeutic purposes, are examples of such applications.

A number of draft documents that describe the main practices involving the use of ionizing radiation in nuclear medicine have already been prepared. Most of these have been produced at the national level. These initiatives are to be commended, and they indicate that there is a global demand for these types of document. Unfortunately, most of these documents tend to be specifically directed towards ensuring compliance with national legislation, and they often lack practical information regarding accepted practice. It is felt that Member States would benefit significantly from the availability of specific information on the implementation of QA programmes that addresses the different factors that may influence the radioactivity delivered to patients in nuclear medicine facilities.

Practitioners in a particular field must apply these QA programmes within their own management systems to fulfil their own specific requirements or ensure compliance with existing national regulations. This requires a degree of 'interpretation' by the user that can result in varying levels of compliance (or non-compliance) and inconsistencies between similar practices. Therefore, there appears to be scope for producing a harmonized set of principles. This report aims to fulfil this need.

1.2. OBJECTIVE

The aim of this framework QA programme is to provide information specific to the administration of unsealed radionuclides in nuclear medicine in a way that is consistent with international guidelines such as ISO/IEC 17025 [4]. Within this report, therefore, the main inputs address the management requirements as well as the technical requirements contributing to the determination of delivered dose — the radionuclidic purity, the chemical form and the amount of radioactivity. The intention of this report is not to repeat basic requirements such as those from GS-R-3 [2] and the BSS [1] or equivalent national regulations, but to provide complementary information. In cases of apparent conflict between the principles included herein and established national legislation or nationally accepted practice, the latter must prevail.

It is recognized that control of the delivery of radioactivity to the patient is only one component of the practice of nuclear medicine. Therefore, the principles in this report are to be regarded as only one part of an overall QA scheme that encompasses the entire nuclear medicine practice. Thus, it is desirable that guidance for QA practices in other aspects of nuclear medicine and radiopharmacy also be consulted.

1.3. SCOPE

The principles in this report are intended for use by regulators, secondary standards radioactivity laboratories (SSRLs), providers of radiopharmaceuticals (including manufacturers) and end users (nuclear medicine physicians, nuclear medicine technologists, etc.). They can be used by regulators in the review of applications for authorization and during facility inspections. Secondary standards radioactivity laboratories may follow them closely or propose alternative measures that provide an equivalent level of accuracy, consistency and QA. End users will also find in this report simplified procedures that, while not necessarily resulting in the same levels of accuracy and precision as procedures implemented in SSRLs, are appropriate to provide sufficient confidence at a level suitable for more routine applications (such as at clinical centres).

2. NORMATIVE REFERENCES

Parties who wish to apply the principles in this report are encouraged to investigate the possibility of using the most recent editions of the following normative publications:

- (a) International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources [1];
- (b) The Management System for Facilities and Activities, IAEA Safety Standards Series No. GS-R-3 [2];
- (c) Application of the Management System for Facilities and Activities, IAEA Safety Standards Series No. GS-G-3.1 [3];
- (d) General Requirements for the Competence of Testing and Calibration Laboratories, ISO/IEC 17025 [4];
- (e) Quality Management Systems — Requirements, ISO 9001:2000 [5];
- (f) International Vocabulary of Basic and General Terms in Metrology [6];
- (g) Proficiency Testing by Interlaboratory Comparisons — Part 1: Development and Operation of Proficiency Testing Schemes, ISO/IEC Guide 43-1:1997 [7].

3. TERMS AND DEFINITIONS

For the purposes of this report, the relevant terms and definitions given in the BSS [1] apply. In addition, the following terms have been adopted:

- (a) **Laboratory.** Any qualified entity that has been delegated responsibility for preparing radioactive samples and carrying out radioactivity measurements, either at the end user level, such as a radiopharmacy or nuclear medicine service, or at the SSRL level.
- (b) **Secondary standards radioactivity laboratory (SSRL).** Any qualified entity that has been delegated responsibility for the preparation and calibration of standardized radioactivity samples that has established measurement traceability to a national metrology institute (NMI) that holds primary standards for radioactivity (or the equivalent, as recognized by the Bureau international des poids et mesures (BIPM)).
- (c) **Customer/client.** Any entity contracting with a laboratory for the provision of radioactivity measurement services. This includes the nuclear medicine physician, technician or other individual (or his or her organizational unit) requesting the measurement (at the end user level), or a radiopharmacy or nuclear medicine service in the case of an SSRL.
- (d) **Radiopharmaceutical.** Any chemical compound containing a radioactive atom that is administered to humans for the purpose of diagnosing or treating a disease or physiological condition. Radiopharmaceuticals are to be considered chemically and biologically the same as any other drug, with additional precautions taken because of the presence of the radioactivity.

4. MANAGEMENT SYSTEM REQUIREMENTS

4.1. ORGANIZATION

The laboratory or its parent organization needs to be legally accountable for the activities being conducted. For most practices described in this report, the ability to legally carry out the work requires that the appropriate permission (licences, registrations, etc.) be obtained from the relevant national regulatory authority.

The laboratory must be committed to an effective quality policy, particularly at the senior level, and must provide clear demonstrable support for those persons with direct responsibility for implementation of the QA programme. This commitment needs to be expressed in a written policy statement that clearly assigns prime importance to implementation of the QA programme in the nuclear medicine services, while recognizing that the prime objective is the medical care of the patients. To support this commitment, it is important that appropriate resources be made available, a QA programme be established as an integral part of the management system and a safety culture be fostered within the organization.

The laboratory needs to define and document the organization hierarchy and management structure. Personnel with particular responsibilities, including the quality manager (however named) and the technical manager (however named), need to be appointed. The organization may decide that the management system can be overseen most beneficially by one or two individuals or by a group. For the purposes of this report, that group is usually designated as the quality assurance committee (QAC).

It is important that the laboratory assign clear responsibilities and authorities to personnel² to ensure adequate safety of administered patient radioactivity. The need for qualified experts must be determined, their responsibilities defined and suitable persons appointed on either a full or part time basis.

The laboratory must establish a comprehensive management system that includes a QA programme for radiation measurement, radiation protection, safety and image quality to ensure that all necessary procedures are developed and implemented to comply with the regulations for radiation protection within the terms and conditions of the authorization(s) of the facility. The management system will enable review and assessment of the overall effectiveness of the protection and safety measures.

It is important that the QA programme cover the entire process, from the initial decision to adopt a particular procedure to the interpretation and recording of results, and that it include ongoing auditing, both internal and external, as a systematic control methodology.

² In the case of the end user, personnel include medical practitioners, nuclear medicine physicists, nuclear medicine technologists, radiopharmacists, radiation protection officers and other health professionals; for an SSRL, personnel include chemists, technicians, physicists and other personnel associated with preparing, calibrating and disseminating calibrated radioactivity standards.

Safety is a vital component of all management systems, and a radiation protection programme needs to be implemented in every laboratory dealing with radioactivity measurement. The radiation protection programme will overlap the QA programme extensively with respect to quality control (QC) of physical factors in medical exposure, as established in the BSS; moreover, the corresponding committees responsible for their implementation (i.e. the QAC and radiation safety committee) may also have members in common.

Radiation protection issues must be given the importance required by regulations. Thus, procedures that establish a mechanism for direct reporting to management are necessary.

For clinical nuclear medicine, it is expected that the guidelines of appendix II of the BSS regarding medical radiation exposure will be followed. This implies that the proposed medical procedure is justified, appropriate for the indication and carried out by competent personnel.

For operations relating to SSRLs, it is expected that all relevant safety guidelines will be observed. Following properly designed procedures concerning source preparation, calibration, standardization and shipping will help to ensure that radiation exposure is minimized.

4.2. QUALITY ASSURANCE PROGRAMME

One important aspect of any QA programme is continuous quality improvement. This implies a commitment by the staff to continuously strive to improve the use of unsealed sources in diagnosis and therapy based on new information learned from the QA programme and new techniques developed by the nuclear medicine community at large. Feedback from operating experience and lessons learned from accidents or averted accidents can help to identify potential problems and correct deficiencies, and therefore their systematic use as part of the continuous quality improvement process is to be encouraged. Guidance on continuous improvement can be found in Ref. [3].

With regard to radioactivity measurements in nuclear medicine, it is important that QA cover at least the following:

- (a) Acceptance, commissioning and QC of equipment and software;
- (b) QC of radiopharmaceuticals, radionuclide generators and other unsealed radionuclides;
- (c) Measurements of the physical parameters of all equipment at the time of commissioning and periodically thereafter;

- (d) Verification of the appropriate chemical and physical factors (e.g. amount of radioactivity, radiopharmaceutical composition) used in patient diagnosis or treatment;
- (e) Review of the procedures, taking into account the clinical factors that may influence the results;
- (f) Written records of relevant procedures and results;
- (g) Verification of the appropriate calibration and conditions of operation of the radionuclide activity calibrator;
- (h) Verification of the quality of the prepared radiopharmaceutical;
- (i) Reporting;
- (j) Training and continuing education of staff;
- (k) Clinical audit and interlaboratory comparison;
- (l) General outcome of nuclear medicine service.

4.3. DOCUMENT CONTROL

The maintenance of management documents and records is an important part of the QA programme, and the management system's documentation needs to be communicated to, understood by, available to and implemented by the appropriate personnel. The organization must establish and maintain procedures to control all documents that form part of its management system. This includes those generated internally and those from external sources, such as regulations, standards, other normative documents, and test and/or calibration methods, as well as drawings, software, specifications, instructions and manuals. Ideally, the person responsible for the overall operation of the QA programme, the quality manager (QM), will identify and provide to the QAC a list of tasks related to QA that need written procedures. The QAC will then establish the person(s) responsible for drafting and signing each procedure and for teaching the procedure to the users, where appropriate. The QAC and the QM will maintain a file with copies of all procedures.

All changes are to be reviewed and approved by the group that performed the original review, unless other personnel are specifically designated. The designated personnel must have access to pertinent background information upon which to base their review and approval.

The procedure(s) adopted must ensure that:

- (a) Authorized editions of appropriate documents are available at all locations where operations essential to the effective functioning of the nuclear medicine facility are performed;

- (b) Documents are periodically reviewed and, where necessary, revised to ensure continuing suitability and compliance with applicable requirements;
- (c) Invalid or obsolete documents are promptly removed from all points of issue or use, or otherwise assured against unintended use;
- (d) Obsolete documents retained for either legal or knowledge preservation purposes are suitably marked.

It is desirable that the altered or new text be identified in the document or the appropriate attachments. Guidance on document control can be found in Ref. [3].

4.4. REVIEW OF REQUESTS, TENDERS AND CONTRACTS

4.4.1. Providers of calibrated radioactive sources

The use of calibrated radioactivity standards is a necessary part of the management system. Ensuring that the sources are prepared correctly and according to the user's specifications can help to minimize unnecessary radiation exposure. Because the capabilities of each laboratory are likely to be different, it is important that each facility decide upon the products and services that it will provide based on a review of its capabilities. In turn, clients need to be made aware of the laboratory's capabilities and any limitations on the services that can be provided.

In requesting a measurement service (calibration, standardized sources, etc.), the customer needs to specify as completely as possible the requirements for and intended use of the service. Ideally, the formal request will include the following information (where relevant):

- (a) Identity of requestor, including name of authorized individual responsible for the request;
- (b) Name(s) of radionuclide(s);
- (c) Amount of radioactivity, including units;
- (d) Reference time for measurement;
- (e) Chemical form and physical configuration of source;
- (f) Type of instrument, and model and serial numbers (if the request is for calibration);
- (g) Physical quantities to be calibrated and range of variables over which calibration is required (e.g. calibration of radionuclide activity calibrator for activity over the range from 100 kBq to 1 GBq for energies over the range from 141 to 1000 keV).

4.4.2. End users of radiopharmaceuticals and radioactive devices

This report assumes that medical radiation exposures from unsealed radionuclides are justified by weighing the diagnostic or therapeutic benefits they produce against the radiation detriment they might cause, taking into account the benefits and risks of available alternative diagnostic techniques that may or may not involve medical exposure (e.g. X ray, computed tomography (CT), ultrasound or magnetic resonance imaging (MRI)), or the benefits and risks of available alternative therapeutic techniques that may or may not involve ionizing radiation exposure (e.g. external beam radiotherapy, drug therapy or surgery). Such a decision is generally made by the attending nuclear medicine (or similarly qualified) physician, based on experience and training, and is governed by acceptable medical practice and safety guidelines such as the BSS.

Each request for administration of radionuclides needs to include at least the following information:

- (a) Name of patient;
- (b) Name of procedure;
- (c) Indication for procedure;
- (d) Date and time of procedure if different from date and time of calibration;
- (e) Name of prescribing physician or authorized user.

The following information must be also supplied in the patient record if it is not included in the administration request:

- (a) Name of radionuclide;
- (b) Name of radiopharmaceutical or chemical form;
- (c) If applicable (particularly for receptor ligands, chiral molecules, colloids and macro-aggregated albumin):
 - (i) Required mass or specific activity;
 - (ii) Conformal isomer;
 - (iii) Number of particles;
 - (iv) Size of particles.

When reporting an activity measurement value, the BSS [1] specify that “unsealed sources for nuclear medicine procedures [shall] be calibrated in terms of activity of the radiopharmaceutical to be administered, the activity being determined and recorded at the time of administration” (BSS, para. II.19(d)) and that “the calibration of sources used for medical exposure be traceable to a Standards dosimetry laboratory” (BSS, para II.19(a)). Guidance on procurement documentation can be found in Ref. [3].

4.5. SUBCONTRACTING OF TESTS AND CALIBRATIONS

When a laboratory subcontracts work, whether for unforeseen reasons (e.g. workload, need for further expertise or temporary incapacity) or on a continuing basis (e.g. through permanent subcontracting, agency or franchising arrangements), competent subcontractors must be selected. A competent subcontractor is one that, for example, complies with the principles included in this report or a similar accepted standard, as well as with the regulatory requirements of the country.

The laboratory needs to advise the client of the subcontractor arrangement in writing and, where appropriate, gain the approval of the client, preferably in writing.

The laboratory is responsible to the client for the subcontractor's work, except in the case where the client or a regulatory authority specifies which subcontractor is to be used.

It is advisable for the laboratory to maintain a register of all subcontractors that it uses for tests and/or calibrations and a record of compliance with the principles included here for the work in question.

4.6. PURCHASE OF SERVICES AND SUPPLIES

It is highly desirable for the laboratory to have a policy and procedure(s) for the selection and purchase of the services and supplies it uses that affect the quality of the test(s) and/or calibration. Procedures need to be in place for the purchase, receipt (particularly with regard to safety inspection) and storage of radionuclides and consumable materials relevant for the tests and calibrations.

It is important to note that some consumable supplies are critical to the accuracy of the measurements of radioactivity. For example, the geometry, chemical composition and dimensions (especially wall thickness) of the container (vial, syringe, etc.) may have a significant effect on the radioactivity measurement. It is important, therefore, to completely specify such equipment and verify that it meets the requirements upon delivery. For suppliers of radiopharmaceuticals, it is important that the end user be notified of any changes in the container, such as a change in the type of vial in which the drug is delivered. Such a change may affect calibrations derived from previous shipments of the drug in other types of container.

The laboratory must ensure that the purchased supplies and radionuclides are not used until they have been inspected or otherwise verified as complying with the standard specifications or requirements defined in methods

for the tests and/or calibrations concerned. It is important that records of actions taken to check compliance be maintained.

4.6.1. Equipment and services

The following principles apply to all equipment and instrumentation used in the delivery of radioactivity measurement services at both the SSRL and end user levels.

The design of the facility and consequent purchase of equipment must take into consideration the type of work intended to be done and the types and activities of the radionuclides intended to be used.

Ideally, written methods will be developed, with the involvement of the responsible staff (e.g. the medical physicist) and possibly the QAC, for the purchase, installation, acceptance, commissioning, use, maintenance and QC of equipment and radiopharmaceuticals and other unsealed sources.

The manufacturer's operating manual must be available in a language understood by the operators.

Before submission to management, all purchase proposals need to be discussed in the QAC, which will: supervise the specification of the equipment; identify possible increases in staff needed to properly handle the new equipment; establish all necessary additional education and training, and new procedures; and review the maintenance programme from the point of view of safety.

The set of tests to be used for acceptance of the equipment is to be specified in the purchase conditions.

4.6.2. Radioactive sources

Radioactive sources must be tracked from receipt to transfer or disposal to ensure accountability; to identify when licensed material could be lost, stolen or misplaced; and to ensure that source activity limits authorized in the licence are not exceeded. The activities listed below are to be carried out following approved procedures only:

- (a) **Opening of package.** Procedures must include visual inspection of the package, monitoring of external radiation levels and possible removable contamination, verification that contents agree with packing slip and order record, and monitoring of the packing material and the empty package;
- (b) **Check of sources.** Procedures must include means of safely handling sources and verifying their activity.

4.7. SERVICE TO THE CLIENT

Where laboratories are not the end users of their products (i.e. if they provide calibration services for other entities), they must cooperate with the client to clarify the request and follow up to ensure that the needs were met.

4.8. COMPLAINTS

The laboratory must have a policy and procedure for the resolution of complaints received from clients or other parties. Records need to be maintained of all complaints and of the investigations and corrective actions taken by the laboratory.

4.9. CONTROL OF NON-CONFORMING TESTS

It is advisable that the laboratory, in consultation with workers through their representatives (if appropriate), include in the local rules and procedures the values of all relevant warning or action levels and the procedure to be followed in the event that any such value is exceeded. These procedures will include those situations where measurement assays are to be halted until the problem is resolved.

Table 4 in Appendix VII includes an example of pass/fail criteria for acceptance or rejection of performance checks for radionuclide activity calibrators.

Warning and action levels serve as a tool for determining the integrity of existing procedures and performance. An exceedance of either of these levels signals the need to review the situation to determine the cause.

The QM must conduct formal investigations whenever:

- (a) At the end user level, any of the operational parameters related to administered patient dosage are out of the normal range established for operational conditions;
- (b) At the SSRL level, any abnormal condition leading to erroneous measurement results is present.

The investigation must be initiated as soon as possible following the event, and a written report must be prepared concerning the cause, corrective actions and instructions or recommendations to avoid recurrence. Incidents involving patient exposure must be investigated in accordance with the

requirements set out in appendix II of the BSS [1]. For events related to clinical use, an investigation must be carried out that includes determination or verification of any doses received, and the results must be included in the report.

The report is to be submitted to the QAC and other concerned bodies, as required, as soon as possible after the investigation, or as otherwise specified, and kept for at least three years (or other period, as appropriate). Guidance on control of non-conforming items can be found in Ref. [3].

4.10. CORRECTIVE ACTION

It is advisable for the laboratory to establish a policy and procedure, and to designate appropriate authorities for implementing corrective action when non-conforming work or departures from policies and procedures in the quality system or technical operation have been identified.

Identification of non-conforming work or problems with the quality system or with measurement activities can occur at various places within the quality system and technical operations. Examples are customer complaints, QC, instrument calibration, checking of consumable materials, staff observations or supervision, measurement report checking, management reviews and internal or external audits.

The procedure for corrective action starts with an investigation to determine the root cause(s) of the problem.

When corrective action is needed, the laboratory must identify potential corrective actions and select and implement those most likely to eliminate the problem and to prevent recurrence. The degree of corrective action must be appropriate for the magnitude and risk of the problem.

Any required changes resulting from corrective action investigations need to be implemented and documented. It is advisable that the results be monitored to ensure that the corrective actions taken have been effective. Guidance on corrective action can be found in Ref. [3].

4.11. PREVENTIVE ACTION

Needed improvements and potential sources of non-conformance, either technical or concerning the quality system, must be identified. If preventive action is required, action plans are to be developed, implemented and monitored to reduce the likelihood of the occurrence of such non-conformance and to take advantage of the opportunities for improvement.

Procedures for preventive actions are to include the initiation of such actions and application of controls to ensure that they are effective.

4.12. CONTROL OF RECORDS

The laboratory must establish and maintain procedures for identification, collection, indexing, accessibility, filing, storage, maintenance and disposal of quality and technical records. Quality records ideally will include reports from internal audits and management reviews, as well as records of corrective and preventive actions.

All records must be legible and must be stored and retained in such a way that they are readily retrievable in facilities that provide a suitable environment for preventing damage or deterioration and loss.

It is advisable that the laboratory have procedures to protect and back up records stored electronically and to prevent unauthorized access to or amendment of these records.

The laboratory needs to retain, for a defined period (typically five years), records of original observations, derived data and sufficient information to establish an audit trail, calibration records and a copy of each test report or calibration certificate issued. The records for each test or calibration must contain sufficient information to facilitate, if possible, identification of factors affecting the uncertainty of measurements and to enable the test or calibration to be repeated under conditions as close as possible to the original conditions. The records must include the identities of the personnel responsible for the sampling, performance of each test and/or calibration, and checking of the results.

Observations, data and calculations must be recorded at the time they are made and must be assignable to a specific task.

When mistakes occur in records, each mistake is to be crossed out — not erased, made illegible or deleted — and the correct value entered alongside it. All such alterations to records are to be signed or initialled by the person making the correction. In the case of records stored electronically, equivalent measures are to be taken to avoid the loss or alteration of original data, as well as to identify when and by whom a required change is made.

4.13. INTERNAL ASSESSMENTS

Internal assessments of activities must be carried out according to a predetermined schedule (typically yearly) to verify that operations continue to

comply with the requirements of the quality system and the principles included here. Ideally, the internal assessment programme will address all elements of the management system, including the availability of written records of relevant procedures and results from testing and/or calibration activities. It is the responsibility of the QM to plan and organize audits as required by the schedule and requested by management. Such assessments must be carried out by trained and qualified personnel who are, wherever resources permit, independent of the activity to be audited.

When findings cast doubt on the effectiveness of the operations or on the correctness or validity of the nuclear medicine facility's test or calibration results, the laboratory must take timely corrective action and must notify clients in writing if investigations show that the nuclear medicine facility results may have been affected.

The area of the activity audited, the audit findings and corrective actions that arise from them must be recorded.

Follow-up activities need to verify and record the implementation and effectiveness of the corrective actions taken.

It is desirable that the assessment programme include at least an audit of measurements and verification of physical parameters at the time of commissioning and periodically thereafter, as well as the appropriate calibration and conditions of operation of dosimetry and monitoring equipment. A sample audit programme can be found in Appendix I.

4.14. MANAGEMENT SYSTEM REVIEWS

In accordance with a predetermined schedule and procedure, a review of the facility's management system and testing and/or calibration activities is to be conducted periodically (typically yearly) to ensure their continued suitability and effectiveness, and to introduce necessary changes or improvements. Such a review will take into account:

- (a) The suitability of policies and procedures;
- (b) Reports from managerial and supervisory personnel;
- (c) The outcome of recent internal audits;
- (d) Corrective and preventive actions;
- (e) Assessment by external bodies;
- (f) The results of interlaboratory comparisons or proficiency tests;
- (g) Changes in the volume and type of work;
- (h) Client feedback;

- (i) Complaints;
- (j) Other relevant factors, such as QC activities, resources and staff training.

Findings from management system reviews and the actions that arise from them are to be recorded. Management must ensure that these actions are carried out on an appropriate and agreed timescale.

5. TECHNICAL REQUIREMENTS

5.1. GENERAL

Many factors determine the correctness and reliability of the tests and/or calibrations performed by a laboratory involved in radioactivity measurement. These factors include:

- (a) Personnel;
- (b) Accommodation and environmental conditions;
- (c) Test and calibration methods and method validation;
- (d) Equipment;
- (e) Measurement traceability;
- (f) Sampling;
- (g) Handling of test, measurement and calibration items.

Each of these items is addressed in turn in the following sections.

5.2. PERSONNEL

All personnel on whom protection and safety depend must have the appropriate qualifications and training so that they understand their responsibilities and perform their duties with proper judgement and according to defined procedures.

Individuals in key positions — that is, those responsible for protection and safety and those who could substantially affect protection and safety by virtue of tasks involving manipulation of sources or operation of equipment — must have documented evidence of appropriate education and training. In nuclear medicine, these individuals are:

- (a) Medical practitioners working with radionuclides (e.g. nuclear medicine physicians and other appropriately trained clinical specialists);
- (b) Radiopharmacists working in the nuclear medicine facility;
- (c) Medical physicists working in nuclear medicine (qualified experts in nuclear medicine physics);
- (d) Other health professionals involved in the clinical use of radionuclides (e.g. nuclear medicine technologists);
- (e) Radiation protection officers;
- (f) Staff performing special tasks (e.g. type testing of equipment, QC tests).

For activities conducted in an SSRL, the personnel include:

- (a) Scientific staff and technicians that prepare both radioactive and non-radioactive stock solutions (e.g. acid/base dilutions, carrier solutions), prepare radioactive counting sources and collect measurement data;
- (b) Scientific staff responsible for analysis and reporting of measurement results;
- (c) Radiation protection officers.

To obtain personal accreditation, the staff listed above must have the following qualifications and training, as applicable:

- (a) A university degree or academic qualification relevant to the profession, issued by the competent education authorities as required in the country.
- (b) Accreditation to practise the profession granted by the competent authorities or other institutions as required in the country.
- (c) A course on radiation protection whose contents, methodology and teaching institution are approved by the regulatory authority. This course may be part of the curriculums of the professional education above.
- (d) On the job training supervised by professionals with accreditation by the regulatory authority. This training must include the full range of tasks and professional activities in which the individual will be engaged.

The practical training must include competence assessments and must be documented by other qualified personnel.

The laboratory needs to ensure that staff are aware of:

- (a) The conditions, including limits, of the licence (or registration) authorizing possession and use of radioactive materials;
- (b) Reviews and analysis of incidents and accidents that have occurred in the institution or elsewhere;

- (c) The institution's QA programme and QC procedures;
- (d) The proper use and operation of equipment;
- (e) All relevant radiation safety procedures.

This training must be completed before commencement of duties and is to be updated as required by the QAC. Furthermore, the instruction of personnel will be required whenever significant changes occur in duties, regulations, the terms of the licence or radiation safety procedures.

It is extremely important that the laboratory establish a policy that encourages and/or provides continuing education and a programme of professional development.

The laboratory needs to prepare and keep a record of the initial and periodic instruction of personnel. These records must include the date, the location and a description of the topic of each didactic course. The records are to be kept for at least five years after the expiration of the corresponding authorization. An example of a training and experience record is given in Appendix II.

It is desirable that the laboratory maintain current job descriptions for managerial, technical and key support personnel involved in tests and/or calibrations.

5.3. ACCOMMODATION AND ENVIRONMENTAL CONDITIONS

It is extremely important that nuclear medicine facilities be such as to facilitate correct performance of the tests and/or calibrations.

The laboratory must ensure that the environmental conditions do not invalidate the results or adversely affect the required quality of any measurement. The technical requirements for accommodation and environmental conditions that can affect the results of tests and calibrations must be documented.

The laboratory must aim at maintaining biological sterility, a dust free environment and a steady electricity supply, and due attention must be paid to environmental conditions such as electromagnetic disturbances, other sources of radiation, humidity and temperature. Tests and calibrations must be stopped when the environmental conditions jeopardize the results of the tests and/or calibrations.

The laboratory must be designed so as to limit the spread of surface or airborne contamination by the radioactive material as well as unnecessarily high background radiation.

5.4. TEST AND CALIBRATION METHODS AND METHOD VALIDATION

5.4.1. General

Regardless of the purpose of the radioactivity measurement (or associated assay), whether it be for a radiopharmaceutical or unsealed radionuclide to be administered to a patient or for a standardized source to be used to calibrate a radioactivity measurement instrument, the methods and instrumentation used to perform the measurement must be documented and must be appropriate for the intended task. The choice of method will depend on factors such as chemical form, type of radioactive decay, half-life of the radionuclide, activity concentration, container type and volume.

For routine measurements in SSRLs and nuclear medicine facilities, the procedures outlined here and those in published national or international standards and in peer reviewed professional journals can be used as appropriate; however, they must be included and documented in the standard operating procedure of the laboratory. Any modifications to the official procedure must be validated and documented.

5.4.2. Quality control of radiopharmaceuticals

The radiation absorbed dose to a patient or human research subject is a function of the type and amount of radionuclide administered together with the biological behaviour of the radiolabelled compound or radiopharmaceutical and the physical aspects of the organs and tissues in the body. Therefore, the chemical and radiochemical suitability of radiopharmaceuticals have a critical impact.

Radiopharmaceuticals must comply with both radiation and pharmaceutical standards in order to ensure their safe and efficacious use. The in vivo behaviour of the radiopharmaceutical is dependent upon its quality, which demands high standards of radionuclidic, radiochemical and chemical purity or particle sizing of suspensions. Injections must satisfy additional standards for sterility, apyrogenicity and freedom from foreign particulate matter.

The topic of QA of all aspects of radiopharmaceuticals preparation and use is large in scope and could certainly be the basis of an entire book. However, there are many aspects that are critical, regardless of whether one is concerned with the radioactivity aspects, sterility issues or any other part of the process requiring control, and there is considerable overlap in terms of QA and QC programme implementation. For radioactivity related applications and processes, the following procedures apply.

All radiopharmaceutical preparations must be labelled with the following information:

- (a) The radionuclide and chemical form of the preparation.
- (b) The total activity present and the reference time for the activity measurement. The BSS (para. II.19) specify that, when reporting a radioactivity measurement value, “(a) the calibration of sources used for medical exposure [shall] be traceable to a Standards dosimetry laboratory” and “(d) unsealed sources for nuclear medicine procedures [shall] be calibrated in terms of activity of the radiopharmaceutical to be administered, the activity being determined and recorded at the time of administration”.
- (c) The name and location of the manufacturer.
- (d) The expiration date.
- (e) A number or other identifier by which the history of the product can be traced (e.g. batch or lot number).
- (f) If applicable (particularly for receptor ligands, chiral molecules, colloids and macroaggregated albumin):
 - (i) Required mass or specific activity;
 - (ii) Conformal isomer;
 - (iii) Number of particles;
 - (iv) Size of particles.
- (g) In the case of solutions, the total volume (or mass) of the solution.

Whenever possible, radiopharmaceuticals are to be manufactured according to good manufacturing practice [8–10], as applicable, and must comply with relevant international standards for:

- (a) Radionuclidic purity;
- (b) Specific activity;
- (c) Radiochemical purity;
- (d) Chemical purity;
- (e) Pharmaceutical aspects (toxicity, sterility, pyrogenicity, pH and isotonicity).

Records must be maintained for each of the following, as appropriate: radiochemical purity testing, chemical purity and pH determination, biological integrity (e.g. leucocytes, platelets, antibodies), other characteristics (e.g. specific activity, conformational isomeric purity), sterility and apyrogenicity testing, calculations and analytical methods, and materials.

5.4.2.1. *Radionuclidic purity*

Radionuclidic purity is defined as the percentage of the radioactivity of the required radionuclide to the total radioactivity of the source. Standards for radionuclidic purity are included in various national and international pharmacopoeias (see Refs [11, 12]). The primary reasons for seeking radionuclidic purity in a radiopharmaceutical are to avoid unnecessary radiation dose to the patient, to avoid degradation of image quality and to limit errors in measurements in vivo. It is therefore extremely important to strictly control the levels of radionuclidic impurities in radiopharmaceuticals.

It should be noted that measured radionuclidic purity will not be constant, but will depend on the half-lives of the radionuclides involved. Contaminants with longer half-lives than that of the specified radionuclide are potentially more hazardous because they will progressively reduce the radionuclidic purity and may significantly affect the radiation dose to the patient. They may also affect detection and imaging processing.

The responsibility must remain with the manufacturer to examine its products in detail, and especially to examine preparations of short lived radionuclides for long lived impurities after a suitable period of decay. However, in accordance with good practice, users will perform their own impurity analyses whenever feasible.

When a parent–daughter generator system is used, a check must be made on each eluate to ensure that, at the time of patient administration, any breakthrough of the parent into the eluate is below the limit specified in the appropriate pharmacopoeia.

5.4.2.2. *Radiochemical purity*

Radiochemical purity is defined as the percentage of the radionuclide present in the desired chemical form. Standards for radiochemical purity are included in various national and international pharmacopoeias (see Refs [11, 12]). Radiochemical impurities are detected using a two step process. First, radiochemical species are separated based on differences in chemical characteristics (e.g. using chromatography), then the radioactivity associated with each chemical species is assayed using an appropriate radiation measuring device.

It should be noted that radiochemical purity may not be constant, but may change owing to radiolytic decomposition, oxidation–reduction reactions, interactions with contaminants or stopper/container components, or other factors.

The responsibility must remain with the manufacturer to examine its products in detail and especially to examine preparations of radiopharmaceuticals for chemical stability over time to ensure that appropriate radiochemical purity is maintained throughout the stated shelf life. However, in accordance with good practice, users will perform their own impurity analyses whenever feasible.

5.4.2.3. *Chemical purity*

Chemical purity refers to the proportion of the preparation that is in the specified chemical form, regardless of the presence of radioactivity; it can be determined using normal methods of analysis. Standards for chemical purity are included in various national and international pharmacopoeias (see Refs [11, 12]).

In general, chemical impurities in preparations of radiopharmaceuticals are objectionable only if they are toxic, cause undesired interactions (e.g. precipitation) or modify the physiological processes that are under study.

It should be noted that chemical purity may not be constant, but may change owing to oxidation–reduction reactions, interactions with contaminants or stopper/container components, or other factors.

The responsibility must remain with the manufacturer to examine its products in detail and especially to examine the chemical purity of preparations. However, in accordance with good practice, users will perform their own impurity analyses whenever feasible.

5.4.2.4. *Chemical and radiochemical purity: Standards and procedures*

Working in accordance with standard setting bodies, practice guidelines and regulatory agencies, qualified personnel must establish and document criteria for determining the chemical and radiochemical purity of radiopharmaceuticals prepared for clinical use prior to their administration to patients and based on documented or anticipated biological activity.

Nuclear medicine facilities must develop, implement and document standard written procedures for determining the chemical and radiochemical purity of radiopharmaceuticals prepared for clinical use prior to their administration to patients. These procedures are used to establish the chemical form and purity, radiochemical form and purity, amount of the radionuclide in the desired radiochemical form, characterization of major radiochemical impurities and pH of a radiopharmaceutical. In many cases, these purity tests will be defined in accompanying packaging information. If such tests are indicated, then the laboratory must follow the procedures, making certain to

document that they are to be followed. Failure to maintain the required radiochemical quality may result in poor tissue specificity, with subsequent decreased image quality, and avoidable irradiation of non-target tissues or organs.

Chemical and radiochemical purity testing must be completed on each batch or on a statistically significant and relevant sample of each production lot. The results of end product and/or in-process testing must be documented. These results must be evaluated for conformance with established criteria for acceptance of radiopharmaceuticals prepared for clinical use. Acceptance or rejection of a batch must be documented, especially when the product is intended for administration to humans.

Owing to the short physical half-life of radiopharmaceuticals used in nuclear medicine, procedures are carried out using extemporaneous radiopharmaceutical preparations. Typically, an aliquot of a short lived radionuclide such as ^{99m}Tc sodium pertechnetate is combined with a reagent kit to produce the finished radiopharmaceutical for clinical use. This extemporaneous radiolabelling requires that radiochemical analysis be performed on each preparation before any dosages are administered to patients.

5.4.2.5. Pharmaceutical aspects

Because not every individual dosage of short lived radiopharmaceuticals, including ^{99m}Tc and PET pharmaceutical preparations, can be tested for all pharmaceutical parameters (e.g. sterility) prior to administration, emphasis must be placed on QC of the process and procedures. Thus all operating procedures must be documented and strictly observed, and accurate records must be kept. The production environment needs to be routinely monitored for microbiological, particulate and radioactive contamination. All equipment used in the radiopharmacy must undergo routine planned preventive maintenance, and all instruments must be calibrated regularly.

5.4.2.6. Documentation

Documentation for a radiopharmacy ideally will cover pharmaceutical, physical and safety aspects. It must include records of starting materials, stocks of radioactivity, the production process and the distribution of products, and the disposal of radioactive waste. Records of environmental particulate monitoring, radiation monitoring, workstation performance and the calibration of radiation monitors and staff radiation doses are also necessary.

5.4.3. Quality control of standardized calibration sources

All units of radioactive material to be used as calibration sources must be labelled with the following information:

- (a) The radionuclide and chemical form of the preparation;
- (b) The total radioactivity present or radioactivity concentration;
- (c) The reference time for the radioactivity measurement;
- (d) The laboratory preparing the source;
- (e) A number or other identifier by which the history of the product can be traced, for example, batch or lot number;
- (f) In the case of solutions, the total volume (or mass) of the solution.

For the preparation and distribution of radioactive sources intended for use as calibration standards, the primary properties that need to be monitored for QC are chemical stability and radionuclidic purity. In most cases, the solution will be prepared so that the radioactive material remains in its ionic form over the expected useful life of the source.

5.4.3.1. Chemical stability

Solutions intended for use as calibration standards must remain stable over the expected useful life of the source. This requires that the correct chemical environment be established so that the atoms maintain their intended oxidation state and do not form undesired complexes or adsorb to the container walls. A 'carrier solution' containing an acid or base (as appropriate), an excess of non-radioactive ions of the same element and sometimes a buffer is usually prepared in conjunction with dilution of the master solution. These solutions are unsuitable for use as pharmaceuticals.

The composition of the carrier solution depends on the chemistry of the radionuclide and generally varies from case to case, even between NMIs. Advice can be sought from an experienced metrology institute or the peer reviewed literature to determine the most appropriate composition of the carrier solution for each specific case. The adopted composition must be documented and used each time a similar standardized solution of the same radionuclide is prepared.

5.4.3.2. Radionuclidic purity

Impurity radionuclides can have a profound effect on the applicability of a particular standardized source. In some cases, the impurity can emit

radiations that are similar to those of the primary radionuclide, making it impossible to distinguish between the two, even with a high resolution technique such as gamma ray spectrometry. Likewise, the presence of high energy photons emitted from the decay of an impurity can cause anomalous readings in radionuclide activity calibrators. Therefore, the laboratory preparing and calibrating the standardized solution must assay the solution for possible impurities. The ratio of the impurity radionuclide(s) to the primary radionuclide must be reported as part of the calibration certificate.

In both cases, it is often possible to correct for the contribution from the impurity, but its activity must be quantified. This can be done fairly easily for photon emitting radionuclides by using a high purity germanium (HPGe) detector that is calibrated for both energy and efficiency. Information on performing such calibrations is given in Appendix VII.

Impurity radionuclides that undergo pure beta decay are more difficult to assay and often require that the primary radionuclide be allowed to decay to background levels and that the remaining solution be assayed using an appropriate high efficiency technique such as liquid scintillation counting.

5.4.4. Equipment calibration

Quality control of an instrument begins with its selection. The user must decide what functionality and performance are required, and these requirements must be checked against the manufacturer's specifications. The user must understand how the performance is to be assessed and how the appropriate radionuclide sources, phantoms and any other necessary measuring instruments are to be acquired. The supply of spare parts, availability of service manuals and provision of maintenance also need to be considered, as well as the arrangements available for servicing during the expected lifetime of the equipment.

Perhaps the most critical step towards quality maintenance is carrying out acceptance tests independent of the manufacturer, preferably before completing payment for the purchase of the instrument. Not only will such testing ensure that the performance meets the required specification from the outset, but the results of these tests, duly recorded, will also serve as a reference against which to compare future performance. For institutions having little or no experience with the particular instrument, it is advisable that an outside expert be contracted to conduct the tests.

For most equipment it is desirable to define small sets of routine tests, falling into two categories: operational tests to be undertaken every time the instrument is used, and periodic measurements of performance at appropriate intervals, for example, weekly, monthly or quarterly, depending on the

anticipated reliability. Ideally, a QC manual will be available for each type of equipment, specifying the methods and frequency of testing. More detailed information on performance testing can be found in Appendix VII.

The laboratory must furthermore ensure that:

- (a) The calibration of radionuclide activity calibrators and other equipment and sources utilized for the practice of nuclear medicine is traceable to an SSRL or NMI.
- (b) Radionuclides for nuclear medicine procedures are calibrated in terms of the activity of the radiopharmaceutical to be administered.
- (c) Records of calibration measurements and associated calculations are maintained in accordance with the requirements of the regulatory authority.
- (d) The calibrations of the instruments are maintained by a regular QC programme. Ideally, the regulatory authority will promote a regular inter-laboratory comparison programme, administered on either a national or a regional basis. Guidance regarding how the programme should be organized can be found in ISO/IEC Guide 43 [7].
- (e) Manufacturers provide specifications and a type of approval certificate for radiopharmaceutical activity measuring or radioactivity calibration equipment.

5.4.5. Method validation

When standard methods (i.e. those that have been published in international, regional or national standards) are to be used, the laboratory must confirm that it can properly implement these methods before introducing them. If the standard method changes, this confirmation needs to be repeated.

The laboratory must validate non-standard methods, methods designed or developed by the laboratory, standard methods used outside their intended scope and modifications of standard methods in order to confirm that the methods are suitable for the intended use. The validation is to be as extensive as is necessary to meet the needs of the given application or field of application. The laboratory is to record the results obtained, the procedure used for the validation and a statement as to the method's suitability for the intended use.

5.4.6. Estimation of uncertainty in measurement

The laboratory must have and apply procedures for estimating the uncertainty of its measurement values. The degree of rigour needed in the estimation depends on factors such as the requirements of the method, the

requirements of the client and the existence of narrow limits on which decisions on conformance with a specification are based. When estimating the uncertainty in measurement, all uncertainty components that are of importance in the given situation must be taken into account using appropriate methods of analysis, such as the ISO Guide to the Expression of Uncertainty in Measurement (GUM) [13].

5.5. EQUIPMENT

5.5.1. Specifications

Equipment and related software used for testing, calibration and sampling must be capable of achieving the accuracy required and must comply with specifications relevant to the tests and/or calibrations concerned.

A nuclear medicine practice must have at least one radionuclide activity calibrator and adequate equipment for workplace monitoring of all types of radiation and radioactive sources employed.

Equipment must be operated only within the limits and conditions established in the technical specifications and in the licence requirements, ensuring that it will operate satisfactorily at all times with respect to both the tasks to be accomplished and radiation safety.

After equipment installation, it is necessary to conduct acceptance tests to verify that the equipment conforms to the technical specifications certified by the manufacturer. It is advisable that contracts clearly establish the responsibility of suppliers for resolving non-conformances identified during acceptance testing. Ideally, a qualified expert will define the technical specifications and carry out the acceptance testing of the equipment.

5.5.2. Maintenance

It is important that a maintenance strategy be established at the time of equipment purchase; such a strategy is essential to achieving and maintaining short downtimes, high quality examinations, patient and staff safety, measurement accuracy and accident prevention. All maintenance procedures need to be included in the QA programme at a frequency recommended by the QAC (and advised by the equipment manufacturer and the relevant professional body). Servicing is to include a report describing the findings, with these reports being archived as part of the QA programme.

Ideally, maintenance procedures will include consideration of the following:

- (a) Overall management of the maintenance programme is provided by a qualified expert in nuclear medicine physics;
- (b) Service records are maintained throughout the lifetime of the equipment;
- (c) A service contract, including preventive maintenance, is provided by the manufacturer;
- (d) Measures to prevent the use of equipment that is undergoing maintenance or repair are implemented.

5.5.3. Operation

For equipment operation, the manufacturer's operating manual and the institution's procedures manual are to be followed.

An authorized medical physicist must ensure that the equipment is safe for clinical use. Likewise, the responsible technical maintenance person in the SSRL must ensure the proper upkeep of equipment for metrology purposes.

Equipment must be operated only by authorized personnel. Up to date instructions on the use and maintenance of equipment (including relevant manuals provided by the equipment manufacturer) are to be readily available for use by the appropriate nuclear medicine facility personnel.

Records need to be maintained for each item of equipment and related software significant to the tests and/or calibrations performed. It is desirable that the records include at least the following:

- (a) Identification of the item of equipment and its software;
- (b) The equipment manufacturer's name, and the equipment's type identification and serial number or other unique identifier;
- (c) Checks that the equipment complies with the specifications;
- (d) The current location of the equipment, where appropriate;
- (e) The equipment manufacturer's instructions, if available, or reference to their location;
- (f) Dates, results and copies of reports and certificates of all calibrations, adjustments and acceptance criteria, and the due date of the next calibration;
- (g) The maintenance plan, where appropriate, and maintenance log;
- (h) Information about any damage, malfunction, modification or repair of the equipment.

Equipment that has been subject to overloading or mishandling, that gives suspect results or that has been shown to be defective or outside specification limits must be taken out of service. It must be isolated or clearly labelled or marked as being out of service to prevent its use until it has been repaired

and shown by calibration or testing to perform in accordance with the specifications and has been returned to service.

All equipment is to be labelled, coded or otherwise identified to indicate the status of calibration, including the date when last calibrated and the date the next calibration is due.

When intermediate checks are needed to maintain confidence in the calibration status of the equipment, these checks must be carried out according to defined and documented procedures. Where calibrations give rise to a set of correction factors, procedures are to be developed and documented to ensure that copies (e.g. computer software) are correctly updated.

Test and calibration equipment, including both hardware and software, must be safeguarded from adjustments that would invalidate the test and/or calibration results.

The electrical and mechanical safety aspects of the nuclear medicine equipment are important parts of the maintenance programme. Maintenance work is to be authorized by the facility management and performed by persons who are qualified to work on the equipment. This work may be subcontracted, if required.

5.6. MEASUREMENT TRACEABILITY

The BSS (para. II.19(a)) specify that “the calibration of sources used for medical exposure [shall] be traceable to a Standards dosimetry laboratory”.

Traceability is defined as “the property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons, all having stated uncertainties” [6]. A laboratory establishes traceability of its own measurement standards and instruments to the fundamental quantity (SI units) of radioactivity (the becquerel (Bq)) by means of an unbroken chain of calibrations or comparisons linking them to relevant primary standards of measurement. This link is usually achieved by reference to relevant measurement standards held by primary NMIs.

The unbroken chain of comparisons may be achieved in several steps carried out by different laboratories that can demonstrate traceability. Moreover, the primary standard to which the measurement is traceable need not be held by the country in which the laboratory is located, provided that the primary standard is recognized by the BIPM as being equivalent to other primary standards through comparisons. Examples of traceability and unbroken chains of comparison can be found in Appendix VIII.

The calibration of instruments and reference sources must be traceable to a certified standards laboratory and must be verified by a regular QC programme.

Calibration programmes must be established for all equipment and artefacts that have a significant effect on the accuracy or the validity of measurement results.

5.7. SAMPLING

The laboratory needs to have policies and procedures for sampling radioactive substances, materials or products where a part of a substance is used for subsequent testing, measurement or calibration as a representative sample of the whole. The policies must be:

- (a) Available at the location where sampling occurs;
- (b) Based on appropriate statistical methods;
- (c) Controlled to ensure the validity of the test, measurement or calibration.

Personnel will need to receive education and training regarding the sampling plan, policies and procedures prior to the sampling of substances, materials or products.

Where deviations from the sampling plan, policies and procedures are required, these are to be recorded in detail and communicated to the appropriate personnel.

The laboratory must have procedures for recording relevant sampling data and operations, including a description of the sampling procedures, statistical methods, identification of samples, environmental conditions and facility diagrams.

5.8. HANDLING OF TEST, MEASUREMENT AND CALIBRATION ITEMS

The laboratory must have policies and procedures for test, measurement and calibration items, including provisions to protect the integrity of these items and of data during transport, receipt, handling, protection, storage, retention and disposal.

The laboratory needs to have a system for identifying test, measurement and calibration items that includes unique identifiers to ensure that items cannot be confused physically, or when referred to in the written records or

documents that are retained for the lifetime of the item in the nuclear medicine facility.

Upon receipt of test, measurement and calibration items, inspection for conformance with the policies and procedures for handling such items is to be performed. Abnormalities or departures from the normal or specified conditions described in the test, measurement or calibration method need to be recorded.

When an item does not conform, or when there is doubt as to the suitability of an item for test, measurement or calibration purposes, personnel must seek guidance before proceeding and keep a record of the discussion. Similarly, when the test, measurement or calibration requested is not specified in sufficient detail, personnel must seek guidance before proceeding and keep a record of the discussion.

The laboratory must have policies and procedures for avoiding deterioration, loss, damage, mislabelling or adulteration of the test, measurement or calibration item during storage, handling and preparation. The handling instructions normally provided with the item are to be followed. Storage conditions are to be maintained, monitored and recorded. Arrangements need to be in place to adequately store and secure items as necessary to protect their integrity.

5.9. ENSURING THE QUALITY OF TEST AND CALIBRATION ITEMS

The laboratory must have QC procedures for monitoring the validity of the tests and calibrations undertaken. The resulting data must be recorded in such a way that trends are detectable; where applicable, statistical techniques must be applied to the review of the results. This monitoring must be planned and reviewed and may include, but not be limited to, the following:

- (a) Regular use of certified reference material and/or internal QC using secondary reference material;
- (b) Participation in interlaboratory comparisons or proficiency testing programmes;
- (c) Replicate tests or calibrations using the same or different methods;
- (d) Retesting or recalibration of retained items.

Ideally, the national regulatory authority will promote a regular interlaboratory radioactivity measurement comparison programme, and the laboratory

is encouraged to participate in such a programme. Such a programme could be operated at the SSRL level and conducted on a regional basis.

5.10. REPORTING THE RESULTS

The results of each test, calibration or series of calibrations carried out by the nuclear medicine facility must be reported accurately, clearly, unambiguously and objectively, and in accordance with any specific instructions in the test or calibration methods.

Appendix I

**SAMPLE AUDIT OF QUALITY ASSURANCE FOR
NUCLEAR MEDICINE RADIOACTIVITY MEASUREMENTS**

***Note:** Not all areas indicated in these audit notes will be applicable to every licence, and some may not need to be addressed during each audit. For example, areas that do not apply to the licensee's activities need not be addressed, and activities that have not occurred since the last audit need not be reviewed during the current audit.*

Date of current audit: _____ Date of last audit: _____

Date of next audit: _____

Auditor: _____ Date: _____
(Signature)

Management review: _____ Date: _____
(Signature)

Facility: _____ Location: _____

Facility manager: _____

Qualified personnel: _____

Audit history

- (a) Have previous audits been conducted?
- (b) Have records of previous audits been maintained?
- (c) Were any deficiencies identified during previous audits?
- (d) Were corrective actions taken? (Look for repeated deficiencies.)

Organization and scope of programme

- (a) Qualified personnel
 - (i) Are all qualified personnel listed on the facility licence and/or operating plan?
 - (ii) Are job descriptions and/or the scope of practice of all qualified personnel documented in the policies and procedures?
 - (iii) Are records of education and training maintained for all qualified personnel?
 - (iv) Have education and training credentials for all qualified personnel been verified by the original issuers of those credentials?
 - (v) Do the qualified personnel meet the established education and training requirements?
- (b) Are radioactive measurements occurring in multiple places of use? If yes, list the locations.
- (c) Are all locations listed on the licence?
- (d) Have annual audits been performed at each location? If not, explain.
- (e) Describe the scope of the programme (staff size, number of procedures performed, etc.).
- (f) Licensed material
 - (i) Are the radionuclides, chemical form and quantity used in compliance with the authorization?
 - (ii) Does the total amount of radioactive material in the facility's possession require financial assurance? If so, is the financial assurance adequate?
 - (iii) Are any unsealed materials used? If so, are they obtained from a manufacturer or properly licensed organization and/or prepared by qualified personnel?
- (g) Sealed sources
 - (i) Are the sealed sources in the facility's possession as described according to the applicable regulatory authority?
 - (ii) Are copies of sealed source calibration certificates accessible or available on-site?
 - (iii) Are the manufacturers' manuals for operation and maintenance of medical devices available on-site?
- (h) If the places of use have changed, has the licence been amended?
- (i) If control of the licence has been transferred, was prior consent obtained? If bankruptcy has been filed, has the appropriate regulatory authority been notified?

Use by qualified personnel

Compliance is established by meeting at least one criterion under each category.

- (a) Authorized nuclear pharmacist (not required for laboratories involved in calibration/preparation of standards, unless they are also actively involved in radiopharmaceutical production)

- _____ (i) Certified by specialty board
_____ (ii) Identified on radioactive materials licence
_____ (iii) Listed on facility licence

- (b) Authorized user

- _____ (i) Certified by specialty board
_____ (ii) Identified on radioactive materials licence
_____ (iii) Listed on facility licence

- (c) Authorized medical physicist (not required for laboratories involved in calibration/preparation of standards, unless they are also actively involved in radiopharmaceutical production)

- _____ (i) Certified by specialty board
_____ (ii) Identified on radioactive materials licence
_____ (iii) Listed on facility licence

- (d) Radiation safety officer

- _____ (i) Certified by specialty board
_____ (ii) Identified on radioactive materials licence
_____ (iii) Listed on facility licence

Mobile service

- (a) Are services operated in accordance with applicable regulations?
- (b) Is compliance with applicable regulations evaluated and met?
- (c) Are licensed materials delivered only to clients who are authorized to receive them?
- (d) Are measurement instruments checked for proper functioning before being used at each address of use or on each day of use?

Amendments

- (a) Have there been any amendments since the last inspection/audit?
- (b) Have new amendments been incorporated/implemented?
- (c) Have retired amendments been removed from operation but maintained in a historical records file?

Notifications

- (a) Is the appropriate documentation provided to the regulatory authority for qualified personnel (e.g. authorized nuclear pharmacist, authorized medical physicist, radiation safety officer, authorized user) within 30 days of their starting work?
- (b) Is the regulatory authority notified within 30 days if qualified personnel (e.g. authorized user, authorized nuclear pharmacist, radiation safety officer, authorized medical physicist) leave the job or change names, if the licensee's mailing address or name changes without a transfer of control of the licence or if the licensee adds or changes an area of use?
- (c) Have there been any notifications since the last inspection?

Training, retraining and instructions for qualified personnel

- (a) Have qualified personnel been provided with required/adequate instructions?
- (b) Does each individual adequately understand the current policies, procedures and regulations?
- (c) Has a training programme been implemented?
 - (i) Are operating procedures in place?
 - (ii) Are emergency procedures in place?
 - (iii) Is periodic training required and implemented?
 - (iv) Has each supervised user been instructed in the preparation of radiopharmaceutical material, principles and procedures for

radioactivity measurement, equipment usage and administration of written directives, as appropriate?

- (v) Are records of initial and periodic training maintained for each individual?
- (vi) Briefly describe the training programme.
- (d) Are individuals supervised by an authorized user in accordance with the requirements of the regulatory authority?

Radiopharmaceutical preparation, measurement and administration

- (a) Do qualified personnel manage and involve themselves in all aspects of radiopharmaceutical preparation, measurement and administration?
- (b) Radiopharmaceutical measurements
 - (i) Is the radioactivity of each radiopharmaceutical dosage measured prior to clinical use?
 - (ii) Is measurement either made directly or calculated by decay correction?
 - (iii) Are records of the measurement of radioactivity and calibration date and time maintained?
 - (iv) Are measurements performed by qualified personnel?
 - (v) Are measurements performed using qualified equipment?
 - (vi) Does the amount of radioactivity contained in each radiopharmaceutical dosage conform to the request, policy and procedure, and/or prescription within $\pm 10\%$ or other deviation value as specified by the applicable regulation or facility licence requirement?
- (c) Radionuclidic purity
 - (i) Have criteria for radionuclidic purity been established?
 - (ii) Are determinations of radionuclidic purity performed prior to clinical use for all radiopharmaceuticals prepared in-house? Are records maintained?
 - (iii) Are radionuclidic purity data evaluated prior to clinical use for all radiopharmaceuticals from outside vendors? Are certificates of analysis or other vendor specification documents available on-site?
- (d) Chemical and radiochemical purity
 - (i) Have criteria been established for chemical and radiochemical purity?
 - (ii) Are determinations of chemical and radiochemical purity performed prior to clinical use for all radiopharmaceuticals prepared in-house? Are records maintained?
 - (iii) Are chemical and radiochemical purity data evaluated prior to clinical use for all radiopharmaceuticals from outside vendors? Are

certificates of analysis or other vendor specification documents available on-site?

- (e) Administration of radiopharmaceuticals
 - (i) Is a request for administration of radiopharmaceuticals generated prior to each clinical use?
 - (ii) Are requests generated only by authorized individuals? Are all of the individuals authorized to request radiopharmaceutical administration to humans listed on the facility licence or in the policies or procedures?
 - (iii) Is each dosage properly labelled after measuring and before administration?
 - (iv) Are only radiopharmaceuticals that comply with the established acceptance criteria administered?
 - (v) Are radiopharmaceuticals administered only upon request?
 - (vi) Are appropriate records of administrations of radiopharmaceuticals to humans maintained?
 - (vii) Are radiopharmaceuticals only administered by those qualified personnel listed on the facility licence or in the policies and procedures?

Dosage measuring equipment

- (a) Possession, use, calibration and check of instruments to measure activities of photon emitting radionuclides
 - (i) List the instrumentation possessed and used.
 - (ii) Are approved procedures for the use of instrumentation followed?
 - (iii) Are the instruments checked for constancy and proper functioning at the beginning of each day of use?
 - (iv) Are accuracy, linearity and geometry dependence tests performed before initial use and following repair for each instrument?
 - (v) Are accuracy and linearity tests performed annually or at intervals specified in applicable regulations or in the facility licence?
 - (vi) Is appropriate action taken when QC test results outside the limits indicated in Table 4 (Appendix VII) are observed?
 - (vii) Are records maintained, and do they include the required information?
- (b) Instrumentation for alpha or beta emitting radionuclides
 - (i) List the instrumentation used to assay alpha and beta particles.
 - (ii) Are approved procedures for the use of instrumentation followed?
 - (iii) Are the instruments checked for constancy and proper functioning at the beginning of each day of use?

- (iv) Are accuracy, linearity and geometry dependence tests performed before initial use and following repair for each instrument?
- (v) Are accuracy and linearity tests performed annually or at intervals specified in applicable regulations or in the facility licence?
- (vi) Is appropriate action taken when QC test results outside the limits indicated in Table 4 (Appendix VII) are observed?
- (vii) Are records maintained, and do they include the required information?

Preparation of calibrated standards

- (a) Do qualified personnel manage and involve themselves in the preparation, measurement and shipping of calibrated sources?
- (b) Measurement techniques: Are accepted/published procedures used in the dispensing and measurement/calibration of radioactive sources?
 - (i) List the equipment used for the dispensing and weighing of sources.
 - (ii) List the equipment used for the assay of radioactivity.
 - (iii) List the equipment used for the identification and quantitation of radionuclidic impurities.
 - (iv) Are approved procedures for the use of instrumentation followed?
 - (v) Is the equipment checked for constancy and proper functioning at the beginning of each day of use?
 - (vi) Are accuracy, linearity and geometry dependence tests performed before initial use and following repair of each instrument?
 - (vii) Are accuracy and linearity tests performed annually or at intervals specified in applicable regulations or in the facility licence?
 - (viii) Are records maintained, and do they include the required information?
- (c) Interlaboratory comparisons
 - (i) List radionuclides compared with national/regional laboratories since last audit; include measurement geometry, pilot laboratory and results of comparison.
 - (ii) List comparisons piloted since last audit; include radionuclide(s), measurement geometry, participating facilities and results of comparisons.

Non-conforming events: Corrective and preventive action

If non-conforming events have occurred since the last audit, evaluate the incident(s) and procedures for implementing and administering corrective and/or preventive actions using the existing guidance.

Event date _____ Information source _____

Notifications

Regulatory agency

Referring physician

Patient

In writing/by telephone

If notification did not occur, explain why it did not.

- (a) Written reports to the regulatory authorities
 - (i) Were reports submitted to the appropriate agencies within 15 days or within the time specified in applicable regulations or in the facility licence?
 - (ii) Was a copy sent to the attending physician within 15 days or within the time specified in applicable regulations or in the facility licence?
- (b) Corrective action(s) taken
 - (i) Was cause analysis conducted to determine the root cause(s)?
 - (ii) Were corrective actions identified and implemented?
 - (iii) Were the results of implementing corrective actions monitored?
- (c) Preventive action(s)
 - (i) Were improvements and potential sources of non-conformance identified?
 - (ii) Were preventive actions implemented and their effects monitored?
- (d) Records of non-conformance
 - (i) Have records of non-conforming tests or calibrations been maintained?
 - (ii) Were records made at the time that the non-conforming tests and/or calibrations occurred?
 - (iii) Have records been reviewed by management and operators on a periodic basis?

Bulletins and information notices

Are internal audit reports and inspection reports posted or maintained and made available to all personnel? Are personnel aware of these reports and their right to access them?

Audits and findings

- (a) Provide a summary of findings.
- (b) List corrective and preventive actions.

Appendix II

SAMPLE DOCUMENTATION OF REQUIRED TRAINING AND EXPERIENCE

II.1. GENERAL PRINCIPLES

The required training and experience must have been obtained within the seven years preceding the date of the application, or the individual must document having had related continuing education, retraining and experience since the required training and experience were obtained. Complete retraining is neither practical nor necessary in most cases. Examples of acceptable continuing education and experience are:

- (a) Successful completion of didactic review courses that include radiation safety practices relevant to the proposed type of authorized medical use;
- (b) Practical and laboratory experience using radioactive material for the same use(s) for which the applicant is requesting authorization (for clinical use or for standards preparation);
- (c) Practical and laboratory experience under the supervision of an authorized user, or other authorized/qualified individual as appropriate, at the same or another licensed facility that is authorized for the same use(s) for which the applicant is requesting authorization.

The simplest and most straightforward method of demonstrating acceptable training and experience is through certification by a recognized professional board (if available).

TRAINING AND EXPERIENCE

Note: Descriptions of training and experience must contain sufficient detail to match the training and experience criteria in the applicable regulations.

Name of individual, proposed authorization (e.g. radiation safety officer) and applicable training requirements:

Certification (if any)

Specialty board (if any)	Category	Month and year certified
--------------------------	----------	--------------------------

Didactic training

Description of training	Location	Clock hours	Dates of training
-------------------------	----------	-------------	-------------------

Radiation physics and instrumentation:

Radiation protection/radiation biology:

Mathematics pertaining to the use and measurement of radioactivity:

Chemistry of by-product material for medical use:

Other:

Practical experience with radiation (actual use of radionuclides or equivalent experience)

Description of experience	Name of supervising individual(s)	Location	Clock hours and dates	Related radiation safety exam score (if any)
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Formal training

Degree, area of study	Name and location of programme	Dates	Name of approving organization
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The individual named on this form is competent to function independently as an authorized user.

Yes No

Note: Response to this item is applicable to proposed authorized users, authorized medical physicists, authorized nuclear pharmacists or radiation safety officer for the type of medical use requested.

The training and experience indicated above were obtained under the supervision of:

Supervisor's signature _____

Name of supervisor

Mailing address

City

Date

SUPERVISOR STATEMENT

Note: Descriptions of training and experience must contain sufficient detail to match the training and experience criteria in the applicable regulations.

This form must be completed by the individual's supervisor. If more than one statement is necessary to document experience, obtain a separate statement from each supervisor.

Name of individual, proposed authorization (e.g. authorized user) and applicable training requirements:

Supervised experience of above named individual

Radionuclide	Type of use	Number of cases involving personal participation	Location, dates and clock hours of experience
<hr/>			

Supervised experience of above named individual (cont.):

Radionuclide	Type of use	Number of cases involving personal participation	Location, dates and clock hours of experience
<hr/>			

The training and experience indicated above were obtained under the supervision of:

Supervisor's signature _____

Name of supervisor

Mailing address

City

Date

Appendix III

RADIONUCLIDIC PURITY

III.1. SCOPE – MOLYBDENUM BREAKTHROUGH

When ^{99m}Tc is eluted from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator, it is possible that ^{99}Mo could be coeluted. This is termed ‘molybdenum breakthrough’. Molybdenum-99 has a relatively long half-life (66 h) and has high energy beta emissions. It is taken up by the parenchymal cells of the liver when administered to patients. The liver receives a dose of approximately 0.8 cGy/MBq from ^{99}Mo ; for this reason, many national and regional regulatory bodies place limits on the amount of ^{99}Mo allowed in a dosage of a ^{99m}Tc radiopharmaceutical. These limits vary among different countries and regions. For example, the United States Pharmacopeia [12] restricts Mo content to 0.15 kBq of ^{99}Mo per MBq of ^{99m}Tc at the time of patient administration, while the European Pharmacopoeia [11] limits it to 1.0 kBq of ^{99}Mo per MBq of ^{99m}Tc . To ensure that ^{99m}Tc radiopharmaceuticals meet the necessary purity requirements, each elution must be tested for ^{99}Mo .

Analysis for parent breakthrough is to be performed whenever any type of generator having parent–daughter radionuclides in equilibrium is used, including $^{188}\text{W}/^{188}\text{Re}$, $^{68}\text{Ge}/^{68}\text{Ga}$, $^{82}\text{Sr}/^{82}\text{Rb}$, $^{62}\text{Zn}/^{62}\text{Cu}$ and others currently under development. In these cases, however, it is necessary to use a breakthrough shield that is optimized to attenuate the X rays emitted by the parent. Since part of the radiation emitted by the daughter radionuclide comes in the form of an X ray emission similar in energy to the parent X rays, a calibration figure for the daughter in the radiation shield will need to be derived for the radionuclide activity calibrator in order to account for the decrease in response from the attenuation of the daughter X rays.

The $^{90}\text{Sr}/^{90}\text{Y}$ generator poses special problems because both the parent and the daughter are pure beta emitters and are therefore difficult to accurately and consistently measure in radionuclide activity calibrators. In this case, a different technique will need to be developed to permit this type of analysis.

III.2. SAMPLE PROCEDURE FOR ^{99m}Tc

- (1) Ensure that the radionuclide has been properly adjusted for background activity using the manufacturer’s instructions. Most modern radionuclide

activity calibrators have a built-in function for background adjustment, as well as for zero correction.

- (2) Select the ^{99}Mo setting on the radionuclide activity calibrator (this assumes the use of a radionuclide activity calibrator that utilizes preset or user definable calibration settings).
- (3) Place the empty ^{99}Mo assay shield in the radionuclide activity calibrator. Record the background reading.
- (4) Place the elution vial containing $^{99\text{m}}\text{Tc}$ pertechnetate in the ^{99}Mo assay shield.
- (5) Place the shielded vial in the radionuclide activity calibrator and obtain the reading.
- (6) Record the ^{99}Mo activity as output from the radionuclide activity calibrator, corrected, as appropriate, for photon attenuation (note that some radionuclide activity calibrators incorporate photon attenuation correction in their calibration setting for ^{99}Mo).
- (7) Remove the elution vial from the assay shield.
- (8) Assay the elution vial (on the $^{99\text{m}}\text{Tc}$ setting) in an appropriate holder.
- (9) Record the $^{99\text{m}}\text{Tc}$ activity as output from the radionuclide activity calibrator.
- (10) Divide the total ^{99}Mo activity (in kBq) by the total $^{99\text{m}}\text{Tc}$ activity (in MBq) to obtain the ratio (kBq ^{99}Mo)/(MBq $^{99\text{m}}\text{Tc}$). Record the results.
- (11) The information in Tables 1 and 2 can be used to determine the shelf life of the $^{99\text{m}}\text{Tc}$ elution based on the observed levels of ^{99}Mo . The necessary indicator for using the data in the table is the initial activity ratio (kBq ^{99}Mo /MBq $^{99\text{m}}\text{Tc}$), which is defined as the eluate N value:

$$N = \frac{\text{kBq } (^{99}\text{Mo})}{\text{MBq } (^{99\text{m}}\text{Tc})} \quad (1)$$

III.3. MEASUREMENT OF OTHER RADIONUCLIDIC IMPURITIES IN RADIOPHARMACEUTICALS AND STANDARD SOLUTIONS

III.3.1. Scope

In addition to imparting additional, unnecessary dose to the patient, radionuclidic impurities can negatively affect other aspects of nuclear medicine practice [16]. In particular, the emission of high energy photons from an impurity in an imaging agent can cause blurring and other distortions due to

TABLE 1. ACCEPTABLE SHELF LIFE OF ^{99m}Tc ELUATE AS A FUNCTION OF THE ACTIVITY RATIO OF ^{99}Mo TO ^{99m}Tc (N) ACCORDING TO UNITED STATES PHARMACOPEIA (USP) LIMITS

(data from Refs [14, 15])

N	Shelf life (h)
0.023	18
0.0425	12
0.0472	11
0.0524	10
0.0582	9
0.0647	8
0.0719	6
0.0887	5

TABLE 2. ACCEPTABLE SHELF LIFE OF ^{99m}Tc ELUATE AS A FUNCTION OF THE ACTIVITY RATIO OF ^{99}Mo TO ^{99m}Tc (N) ACCORDING TO EUROPEAN PHARMACOPOEIA LIMITS ^a

N	Shelf life (h)
0.153	18
0.283	12
0.315	11
0.349	10
0.388	9
0.431	8
0.479	6
0.591	5

^a European Pharmacopoeia limit = $6.66666 \times N(\text{USP})$.

incomplete collimation of the image resulting from photons penetrating the collimator septa. One example is the case of ^{201}Tl , which decays primarily with the emission of a 167.43 keV gamma ray and is widely used as a cardiac imaging agent. Solutions of ^{201}Tl can contain substantial amounts (up to 2%) of ^{202}Tl , which decays with the emission of a 439.46 keV gamma ray that can easily penetrate a low energy collimator and thereby degrade the image.

Photon emitting impurities can also have a strong influence on the reading of the primary radionuclide in radionuclide activity calibrators, particularly if the impurity decays with the emission of high energy photons. For this reason, the assay of possible parent breakthrough from generators or other radionuclidic impurities is important in the preparation of standards and calibration sources.

III.3.2. Impurity analysis using HPGe detectors

The most accurate method for assessing and quantifying the presence of photon emitting impurities is spectral analysis using high resolution HPGe detectors. A diagram of a typical HPGe counting system is shown in Fig. 1.

To be able to quantify the main radionuclide and the possible impurities, the detector system (the detector and associated electronics) must be properly calibrated for both energy and efficiency. This is done using either a series of standardized sources, each containing a single nuclide (and having the same configuration) or a single calibrated source containing several gamma emitting radionuclides. Such sources are generally available from an NMI or from

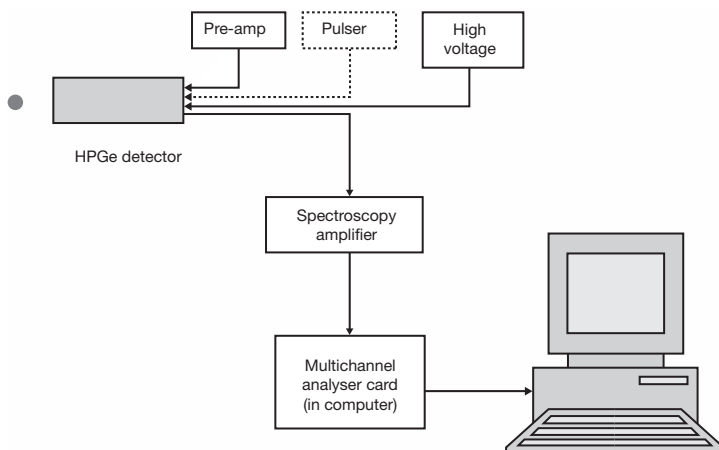


FIG. 1. An HPGe spectroscopy system for gamma rays.

commercial laboratories that can demonstrate measurement traceability to an NMI.

Ideally, the energy range covered by the calibrated sources will also cover the range of energies over which measurements will be made. Recommended radionuclides, along with the decay data necessary to perform the calibrations, can be found in Ref. [17].

Most commercial gamma ray spectrometry acquisition and analysis software contains routines for calibrating the detector, and it is advisable for the user to refer to the relevant software manual for specific guidance. In general, the steps required to calibrate the detector for energy and photopeak efficiency are as follows.

III.3.2.1. Simplified procedure for energy calibration

- (1) Using the same source to detector distance and source configuration intended for routine measurement, acquire sufficient counts in the spectrum so as to be able to identify the centroid of the photopeak(s) for which the energy is precisely known.
- (2) If more than one source is required to completely cover the desired energy range, stop data acquisition during source replacement and restart once the new source is in place *without zeroing the spectrum*.
- (3) Once at least five energy points have been taken, use the acquisition/analysis programme's cursor to find the channel number corresponding to the centroid of each peak to be used in the calibration.
- (4) Once the channel numbers and the energies corresponding to the calibration photopeaks are known, a fit of the data to a quadratic polynomial is generally sufficient to provide the necessary accuracy.

III.3.2.2. Simplified procedure for determination of photopeak efficiency

- (1) Using the same source to detector distance and source configuration intended for routine measurement, acquire a background spectrum overnight for a preset counting live time.
- (2) Using the same configuration, measure each of the standardized sources for a sufficient length of time to accumulate 10^6 counts in the main peak(s) of interest. Data are to be collected using a fixed counting live time.
- (3) If multiple single nuclide sources are used, repeat step 2 as needed to acquire spectra for each counting source.
- (4) Subtract the background spectrum from each set of spectra of the standard sources, remembering to normalize the spectra to the same

counting live time. Most spectrum analysis programmes are able to do this automatically.

- (5) Use the peak fitting routine in the analysis software to fit the peaks from the spectra. Most programmes can calculate the counting rate in the peak in units of counts per second.
- (6) The peak energy efficiency, ε_{E_i} , at energy E_i is calculated as

$$\varepsilon_{E_i} = C'_i / (A'_i P_{\gamma_i}) \quad (2)$$

where C'_i is the background corrected counting rate (in s^{-1}) for the peak at energy E_i , A'_i is the decay corrected certified activity (in Bq) of the radionuclide producing the peak at E_i and P_{γ_i} is the emission probability of the gamma ray at E_i .

- (7) The efficiency curve as a function of energy can be fitted to allow for the determination of efficiencies of other gamma rays by interpolation. Most commercially available acquisition software is able to perform this fitting and the interpolation automatically.

In some cases, particularly for highly radioactive samples, it may be necessary to dilute the sample in order to keep the dead time and pile-up at acceptable levels (dead time <10%) during measurement. If dilution is necessary, it is important that it be done in a way that ensures that the diluted sample still accurately represents the original in terms of density and minimum detectability of impurities. In some cases, it may be necessary to allow the original sample to decay for some time so that longer lived, low activity impurities can be measured.

A more detailed discussion of gamma ray spectrometry techniques can be found in Refs [18–21].

Appendix IV

CHEMICAL PURITY – SAMPLE PROCEDURE FOR ALUMINA BREAKTHROUGH TESTING

For clinical applications. Chemical and radiochemical evaluations may include direct testing using chromatographic and/or colorimetric methods; pH measurements; and documentation of the manufacturer's specifications of radionuclides and radiopharmaceuticals, and their components. Specific methods and criteria for acceptance can be found in relevant pharmacopoeias and regulatory guidelines.

For calibration/standardization applications. The amount of possible alumina breakthrough found with most generators is generally not sufficient to affect the solution's use as a calibration standard. Therefore, this test can be omitted if the solution will not be administered to humans.

IV.1. SCOPE

The $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator is constructed with alumina (Al_2O_3) loaded in a glass column. The ^{99}Mo radioactivity is adsorbed on alumina in the chemical form MoO_4^{2-} (molybdate). The amount of alumina used is between 2 and 10 g, depending on the total activity of ^{99}Mo . Aluminium can wash off the column during elution and interfere with the radiolabelling of reagent kits, greatly reducing the labelling efficiency, or it can interact with certain chemical species and result in precipitation or flocculation. Most pharmacopoeias set a limit of 10 μg of aluminium per millilitre of $^{99\text{m}}\text{Tc}$ elution. Standards of good laboratory/manufacturing practice recommend the testing of each elution for aluminium. Each of the tests described below involves the use of standard solutions; the first uses commercially available test kits and the second uses reagents and a UV visible spectrophotometer, which can be found in most analytical laboratories.

IV.2. SAMPLE PROCEDURE A: COMMERCIAL TEST KIT

- (1) Use a commercially available colorimetric aluminium ion test kit.
- (2) Place one small drop of the aluminium standard on an indicator strip. The standard contains 10 μg aluminium per millilitre of solution.

- (3) Draw a small amount of the elution and place a small drop on the indicator strip adjacent to the standard spot. For greatest accuracy, use two spots of the same size.
- (4) Compare the colour intensity of the two spots.
- (5) If the elution spot is more intense or darker in colour than the aluminium standard spot, the aluminium ion exceeds 10 µg/mL. Discard the elution. Record the results.
- (6) If the elution spot is less intense or lighter in colour than the aluminium standard spot, the aluminium ion concentration is acceptable. Record the results.

IV.3. SAMPLE PROCEDURE B: SPECTROPHOTOMETRIC TEST [12]

- (1) Prepare an aluminium standard solution by accurately weighing out 35.17 mg of $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ and dissolving it in 1000 mL of distilled water using a volumetric flask.
- (2) Pipette 10 mL of the aluminium standard solution into each of two 50 mL volumetric flasks; then add three drops of methyl orange test solution (TS) and two drops of 6 N NH_4OH to each flask.
- (3) Add 0.5 N HCl dropwise to each flask until the solutions turn red.
- (4) To one of the flasks, add 25 mL of sodium thioglycolate TS; to the other, add 1 mL of Na_2EDTA .
- (5) Add 5 mL of eriochrome cyanine TS and 5 mL of acetate buffer TS to each flask, and add distilled water to fill to the 50 mL mark on each volumetric flask.
- (6) Immediately measure the absorbance of the solution containing the sodium thioglycolate at a wavelength of 535 nm in a suitable UV visible spectrophotometer, using the solution containing the Na_2EDTA as a blank solution.
- (7) Repeat the procedure using two 1.0 mL aliquots of eluent.
- (8) The concentration (in µg/mL) can be calculated as $C_{\text{Al}} = 20(T_{\text{U}}/T_{\text{S}})$, where T_{U} and T_{S} are the absorbances of the eluent and the aluminium standard, respectively.
- (9) Discard the solution if the C_{Al} is found to be above 10 µg/mL.

Appendix V

RADIOCHEMICAL PURITY TESTING OF ^{99m}Tc RADIOPHARMACEUTICALS

The testing requirements for radiochemical purity of most radiopharmaceuticals encountered in routine use are generally specified in applicable pharmacopoeias. Moreover, commercially available kits for producing radiopharmaceuticals generally contain information on testing requirements and procedures mandated by certain national regulatory bodies (e.g. the United States Food and Drug Administration). Such tests are usually noted in the packaging inserts accompanying the cold kits. The following information is intended to provide the user with examples of the techniques that are applied. Persons who will be responsible for performing these tests on a routine basis are encouraged to seek formal practical training in the use of these techniques.

V.1. SCOPE – THIN LAYER CHROMATOGRAPHY

Thin layer chromatography (TLC) is the method most commonly used to test ^{99m}Tc labelled radiopharmaceuticals for radiochemical purity. The TLC method is simple, fast and inexpensive. A small sample of the radiopharmaceutical is placed on a solid support medium containing the stationary phase. This solid or stationary phase is typically layered onto a support medium such as glass or plastic, or may be impregnated in a glass microfibre mesh (for instant thin layer chromatography (ITLC)). Two common media are silica gel and silicic acid. The solvent, or mobile, phase transports the radiopharmaceutical over the solid phase by adsorption and capillary action.

The various radiochemical species present demonstrate different affinities for the solid and mobile phases and are separated on this basis. The selection of appropriate solid and solvent systems allows the separation of the different chemical species in the radiopharmaceutical.

Radiolabelled insoluble particles such as ^{99m}Tc sulphur colloid, ^{99m}Tc macro-aggregated albumin (MAA) and monoclonal antibodies are tested with a single strip to determine the percentage of free sodium pertechnetate. Since the particles are insoluble, all labelled species will remain at the origin.

Water soluble ^{99m}Tc radiopharmaceuticals require a two strip testing procedure. At least three radiochemical species are typically present:

- (a) The primary ^{99m}Tc radiopharmaceutical;
- (b) Free pertechnetate or $^{99m}\text{TcO}_4^-$;
- (c) Hydrolysed reduced and insoluble $^{99m}\text{TcO}_2$.

Free pertechnetate or $^{99m}\text{TcO}_4^-$ moves with the solvent front in aqueous or organic solvents. Hydrolysed reduced and insoluble $^{99m}\text{TcO}_2$ remains at the origin in all chromatography systems. Water soluble ^{99m}Tc radiopharmaceuticals move with the solvent front in aqueous chromatography systems only. This allows separation of the radiochemical impurities for quantification. Instant thin layer chromatography using an aqueous mobile phase can isolate the hydrolysed reduced and insoluble $^{99m}\text{TcO}_2$ at the origin. Repeating the ITLC procedure using an organic mobile phase (methyl ethyl ketone, acetone or methanol) isolates uncomplexed sodium pertechnetate at the solvent front. Table 3 illustrates the expected results for ITLC using this technique for three common ^{99m}Tc radiopharmaceuticals. A sample procedure for ITLC analysis of ^{99m}Tc -MDP is presented in Section V.2.

Unfortunately, this simple ITLC method does not work for all ^{99m}Tc radiopharmaceuticals. Several ^{99m}Tc radiopharmaceuticals require the use of special TLC strips and solvents in order to provide adequate separation of the radiochemical impurities from the desired ^{99m}Tc radiopharmaceutical. Specific information can be found in the manufacturer's instructions or other published literature.

TABLE 3. EXAMPLES OF ITLC SEPARATION OF RADIOCHEMICAL SPECIES FOR ^{99m}Tc RADIOPHARMACEUTICALS USING ACETONE (ORGANIC) AND SALINE (AQUEOUS) SOLVENTS

Label	Acetone origin	Acetone front	Saline origin	Saline solvent front
Methylene diphosphonate (MDP; medronate)	Hydrolysed reduced TcO_2 + ^{99m}Tc -MDP	Free $^{99m}\text{TcO}_4^-$	Hydrolysed reduced Tc	^{99m}Tc -MDP + free $^{99m}\text{TcO}_4^-$
Macro-aggregated albumin (MAA; albumin, aggregated)	Hydrolysed reduced TcO_2 + ^{99m}Tc -MAA	Free $^{99m}\text{TcO}_4^-$	Hydrolysed reduced Tc + ^{99m}Tc -MAA	Free $^{99m}\text{TcO}_4^-$
Diethylenetriamine-pentaacetic acid (DTPA; pentetate)	Hydrolysed reduced TcO_2 + ^{99m}Tc -DTPA	Free $^{99m}\text{TcO}_4^-$	Hydrolysed reduced Tc	^{99m}Tc -DTPA + free $^{99m}\text{TcO}_4^-$

Solutions intended for use as calibration standards are generally prepared using the $^{99m}\text{TcO}_4^-$ as eluted from the generator. Moreover, the only value of interest in this application is the activity concentration, regardless of the chemical form (assuming that it is stable). Therefore, this test may be omitted for such solutions that have no intended human use.

V.2. SAMPLE PROCEDURE FOR INSTANT THIN LAYER CHROMATOGRAPHY ANALYSIS OF ^{99m}Tc -MDP

- (1) Prepare two ITLC strips as follows: Mark the origin at 1 cm above the bottom of the strip. Mark the solvent front at 1 cm below the top of the strip. Mark a cut line at the midpoint of the strip.
- (2) Place a 1–5 μL sample of the radiopharmaceutical at the origin of each strip.
- (3) Gently place one strip into the acetone solvent and the other strip into the saline solvent, taking care not to splash or submerge the spots.
- (4) Develop each strip until the mobile phase reaches the line marking the solvent front.
- (5) Remove the strips from the solvents.
- (6) Allow the strips to dry.
- (7) Cut the strips at the cut line.
- (8) Count the bottom half of each strip in a gamma counter, on an HPGe detector or in a radionuclide activity calibrator. Record the counts in counts per minute (CPM).
- (9) Count the top half of each strip in a gamma counter, on an HPGe detector or in a radionuclide activity calibrator. Record the CPM.
- (10) Calculate the radiochemical purity as follows:

$$\begin{aligned} \text{(i)} \quad A &= \text{fraction unbound } ^{99m}\text{TcO}_4^- & (3) \\ &= \text{CPM at the top of the acetone strip} / (\text{CPM at the top of the} \\ &\quad \text{acetone strip} + \text{CPM at the bottom of the acetone strip}). \end{aligned}$$

$$\begin{aligned} \text{(ii)} \quad B &= \text{fraction hydrolysed reduced } ^{99m}\text{TcO}_2 & (4) \\ &= \text{CPM at the bottom of the saline strip} / (\text{CPM at the bottom of} \\ &\quad \text{the saline strip} + \text{CPM at the top of the saline strip}). \end{aligned}$$

$$\begin{aligned} \text{(iii) Fraction desired } ^{99\text{m}}\text{Tc-MDP} & \qquad \qquad \qquad (5) \\ & = 1 - (\text{fraction unbound } ^{99\text{m}}\text{TcO}_4^- + \text{fraction hydrolysed reduced} \\ & \quad ^{99\text{m}}\text{TcO}_2), \end{aligned}$$

or, more simply,

$$\text{(iv) Fraction radiochemical purity} = 1 - (A + B). \qquad \qquad \qquad (6)$$

If a gamma camera with a high resolution collimator is available, steps 8 and 9 can be carried out without cutting the strips by placing each strip on a piece of plastic film on the surface of the gamma camera. The different regions can be quantified from the resulting image.

V.3. QUALITY CONTROL – TROUBLESHOOTING

Some problems may be encountered if proper care is not used while performing TLC testing for radiochemical purity. Some common errors leading to invalid purity testing results are listed below:

- (a) Sample spot placed too low on strip: When placed in the solvent, a spot that is too low on the strip will be submerged, which may contaminate the solvent and render false results.
- (b) Sample spot is too large: Organic solvents (e.g. acetone) that are miscible in water may mix with the excess sample material, resulting in streaking of activity up the strip. If a large spot must be used (e.g. counting in a radionuclide activity calibrator), allow the spot to air-dry before placing it in the solvent. In some cases a row of small spots in a line across the strip at the origin may allow better performance than an equivalent amount as one large drop.
- (c) Prolonged air-drying of sample spot: Prolonged air-drying may cause oxidation of the $^{99\text{m}}\text{Tc}$ labelled radiopharmaceutical and produce false chromatography results.
- (d) Contaminated solvents: Solvents must be free of all radioactivity.
- (e) Degraded solvents: Several solvents are hygroscopic (e.g. ethanol, ethyl acetate, HCl). Routine opening and closing of stock bottles, especially in areas of high humidity, results in degradation of the solvent. Repackage solvents in smaller volumes in airtight containers. If possible, seal caps with wax film.

- (f) Spattering: Careless spotting of the sample could result in dispersion of the sample material beyond the strip origin.
- (g) Splashing of solvent: The chromatography must not be moved after the strip has been placed in the solvent. Movement could submerge the spot and retard migration or, worse, contaminate the solvent.
- (h) Contaminated scissors/forceps: Contamination can be transferred to the strip from the scissors/forceps. Always use clean utensils.
- (i) Incorrect solvents or media: Verify that the chromatography system materials are appropriate and valid for the particular radiopharmaceutical being tested.
- (j) Prolonged migration: Care must be taken to remove the strip when the solvent front reaches the front line. If the solvent is allowed to move 'off' the top of the strip, the test must be repeated.

V.4. OTHER QUALITY CONTROL METHODS

A variety of analytic methods have been used in the determination of the radiochemical purity of ^{99m}Tc radiopharmaceuticals. In addition to TLC, these include such techniques as electrophoresis, paper chromatography, gas chromatography, high performance (also called high pressure) liquid chromatography (HPLC) and solvent extraction. Because of its exquisite resolution in component separation, HPLC is generally deemed to be the gold standard. However, its expense, technical complexity and analysis time limit its practicality in busy clinical facilities that prepare ^{99m}Tc radiopharmaceuticals. Hence, simple and rapid TLC methods predominate for the radiochemical purity testing of ^{99m}Tc radiopharmaceuticals.

Solid phase extraction (SPE) is a reasonable option for testing radiopharmaceuticals for which TLC methods are slow and/or provide poor separation of radiochemical species. Solid phase extraction is similar in principle to HPLC in that it involves a solid support medium coupled with a solvent mobile phase. Compared with HPLC, SPE is much cheaper, faster and easier; however, SPE provides lower resolution and is more susceptible to technical artefacts.

Appendix VI

PARTICLE SIZE ESTIMATION OF ^{99m}Tc -MAA

VI.1. SCOPE – ASSESSMENT OF PARTICLE SIZE

Technetium-99m macro-aggregated albumin (^{99m}Tc -MAA) is a particulate radiopharmaceutical that, following intravenous injection, localizes in the lung by physically lodging in small pulmonary arterioles and capillaries. Use of the proper particle size is important to avoid embolization in larger pulmonary arteries. Although the manufacturer is responsible for the size of the particles in the reagent kit, it is advisable that the particle size of the prepared product be verified prior to clinical use.

The size of ^{99m}Tc -MAA particles can be readily assessed by microscopic inspection. It is important that visual estimation of a representative sample of particles be in agreement with applicable standards. For example, the United States Pharmacopeia [12] requires that >90% of the particles be in the range of 10–90 μm and that no particle exceed 150 μm .

VI.2. SAMPLE PROCEDURE FOR MICROSCOPIC INSPECTION OF ^{99m}Tc -MAA PARTICLES

- (1) Obtain a clean, dry haemocytometer etched with a 50 μm grid.
- (2) Place a cover slip on the slide so that it partially covers the V groove at the edge of the slide.
- (3) Place a sample of the ^{99m}Tc -MAA product in the V groove of the slide; use a sufficient amount so that the product flows up the V groove and fills the space between the slide and the cover slip.
- (4) Place the slide on the microscope stage and adjust and focus.
- (5) Visually estimate the size and range of the ^{99m}Tc -MAA particles using the 50 μm grid as a reference (see Fig. 2).

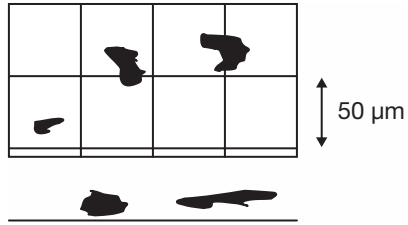


FIG. 2. Illustration of ^{99m}Tc -MAA particles on a $50\ \mu\text{m} \times 50\ \mu\text{m}$ grid haemocytometer.

Appendix VII

MEASUREMENT OF RADIOACTIVITY

VII.1. SCOPE – PROCEDURES FOR DETERMINING RADIOACTIVITY USING RADIONUCLIDE ACTIVITY CALIBRATORS

This procedure details the steps and the associated QA measures necessary for determining the activity of radioactive samples using a radionuclide activity calibrator in the field of nuclear medicine. The steps described here are almost identical to those for preparing secondary standards. In-depth information on the use of ionization chambers for radioactivity measurements can be found in Activity Measurements with Ionization Chambers [22] and the references therein, as well as in A Handbook of Radioactivity Measurements Procedures [19] and several national and international standards [23–25].

VII.2. RADIONUCLIDE RADIOACTIVITY CALIBRATORS

A radionuclide activity calibrator is in essence a well-type gas-filled ionization chamber into which a radioactive material is introduced for measurement. A typical radionuclide activity calibrator is depicted schematically in Fig. 3. The activity of the material is measured in terms of the ionization current produced by the emitted radiations that interact within the gas. The chamber is usually sealed and under pressure, and has two coaxial cylindrical electrodes maintained at a voltage difference from a suitable supply.

In the associated electrometer, the ionization current is processed and finally displayed, commonly in digital form, in units of activity (e.g. becquerels). The processing within the electrometer involves the application of a calibration coefficient that corresponds to the ionization current produced by unit activity of the radionuclide being assayed. Although most radionuclide activity calibrators have such conversion circuits, some older models still in use do not have this feature. In this case, the conversion from ionization current to activity needs to be done manually. The calibration figures are generally provided by the manufacturer and are published in the open literature.

The value of the calibration coefficient depends primarily on the types, energies and abundances of the radiations emitted by the radionuclide. It also depends on the attenuation of these radiations in their passage from the point of disintegration in the sample into the gas volume. The calibration coefficient for an individual radionuclide therefore also depends on the volume and

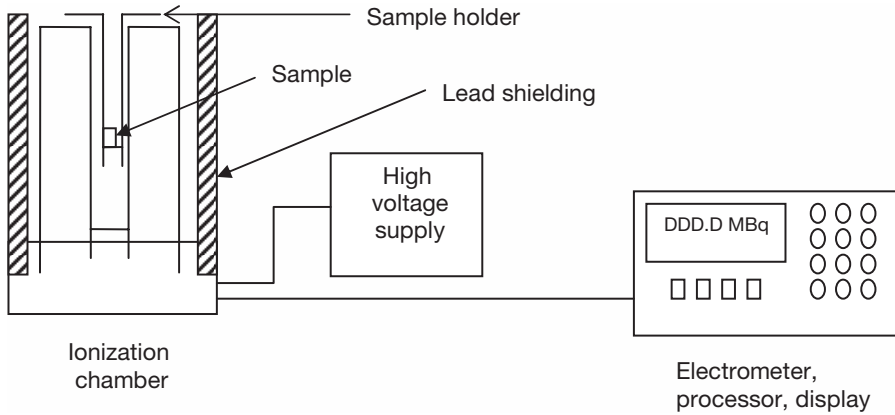


FIG. 3. A typical radionuclide activity calibrator.

physical nature of the sample as well as the container construction and its position within the well of the ionization chamber. It follows that a single calibration coefficient for an individual radionuclide will not be applicable for all of the various samples that may be assayed for that radionuclide.

Lead shielding around the ionization chamber provides protection to personnel against radiation hazards and reduces the response (background) to environmental radiation. A sample holder and a removable liner that can be easily cleaned in the event of radioactive contamination of the chamber well are usually provided. These additional components also influence the quantity of radiation that enters the gas volume, and it is important to recognize that the calibration coefficients only apply when these components are in place. Removal or modification of these components will invalidate the calibration coefficients supplied by the manufacturer.

VII.3. QUANTITIES, RANGES AND ACCURACIES

The quantities to be determined are the activities of radioactive samples expressed in becquerels. The ranges of activities to be measured are nuclide dependent. However, in the nuclear medicine environment, the range of activities to be measured with an accuracy of $\pm 5\%$ or better will typically be between 1 MBq and 10 GBq.

VII.4. EQUIPMENT

In addition to the radionuclide activity calibrator, the necessary equipment may include:

- (a) A mass balance for the accurate dispensing of solutions with an accuracy of at least $\pm 0.1\%$.
- (b) Calibrated volumetric dispensers with a dispensing accuracy of at least $\pm 1\%$.
- (c) Glass vials and septum closures for the containment of radioactive solutions. These need to be specified in terms of dimensions, wall thickness and chemical composition, as they form part of the calibration process.
- (d) Plastic syringes for the dispensing and containment of radioactive solutions. These need to be specified in terms of dimensions, wall thickness and chemical composition, as they may form part of the calibration process.
- (e) Calibrated time-of-day clock.
- (f) Reference sources: sealed (usually in resin) long lived radioactive sources for constancy checks. Typically, the sources contain about 5 MBq ^{137}Cs or 100 MBq ^{57}Co .

In the case of SSRLs, both the balance and volumetric dispensers are to be considered mandatory. For clinics, accurate volumetric dispensers will suffice, although greater accuracy and consistency can be achieved if dispensing is done by mass instead of volume.

VII.5. ENVIRONMENT AND STABILIZATION

Accommodation must be clean and decontaminable, and must prevent radioactive cross-contamination of samples. Shielding around the ionization chamber of the radionuclide activity calibrator will minimize the effect on the sample measurement of other radioactive sources in the vicinity and minimize radiation exposure to those personnel operating the calibrator. Specific guidance is given in IAEA Safety Reports Series No. 40 [26].

VII.6. DESCRIPTION OF PROCEDURES

Specific information on performing routine activity measurements, including measurements of radiopharmaceutical preparations, is given in the following sections.

VII.6.1. Review of request forms

Review the request forms at the beginning of the workday and ensure that all necessary information has been provided. For each preparation/calibration source, the necessary information includes:

- (a) Identification of the radionuclide;
- (b) Activity of the radionuclide at the reference time;
- (c) Reference time;
- (d) Identification of the labelling compound, if any;
- (e) Total volume or mass of each preparation;
- (f) Type of container required (syringe, vial, etc.), including size.

VII.6.2. Daily performance checks

At the beginning of each day of use, conduct the daily QC check of:

- (a) High voltage;
- (b) Zero setting;
- (c) Display;
- (d) Clock;
- (e) Background;
- (f) Check source response;
- (g) Relative responses at the calibration settings for the nuclides to be assayed that day.

The pass/fail criteria are shown in Table 4 in Section VII.7.

VII.6.3. Ongoing performance checks

At the appropriate times (see Table 4, Section VII.7), conduct the relevant ongoing performance checks of:

- (a) High voltage;
- (b) Display;

- (c) Zero adjustment
- (d) Clock accuracy;
- (e) Background;
- (f) Check source response;
- (g) Accuracy (over normal operating range);
- (h) Precision;
- (i) Relative responses;
- (j) Subsidiary calibrations;
- (k) Linearity.

The pass/fail criteria are shown in Table 4 in Section VII.7.

VII.6.4. Measurement of sample activity

The following is a general procedure for routine clinical measurements of radioactivity using ionization chambers.

- (1) Locate the sample and confirm that it corresponds to that identified in the request form.
- (2) Determine the number of readings required for the desired precision.
- (3) Ensure that zero adjustment has been performed according to the manufacturer's instructions.
- (4) Ensure that background correction has been applied according to the manufacturer's instructions. For calibrators that do not have this function, note the background current so that it can be subtracted from the reading, as noted in step 8.
- (5) Enter the appropriate calibration settings into the electrometer (if using a calibrator that has this feature).
- (6) Place the sample in the correct holder(s) and place the holder(s) in the well of the calibrator.
- (7) Start measurements and record time of start and electrometer output for each measurement on the worksheet.
- (8) Apply appropriate corrections for background, decay to reference time, mass/volume and radioactive contaminants. The decay correction is carried out using the equation

$$A_0 = Ae^{\lambda t} \tag{7}$$

where A is the activity at time t , A_0 is the activity at time $t = 0$ (usually taken as the reference time) and λ is the decay constant and is equal to $\ln(2)/T_{1/2}$, where $T_{1/2}$ is the decay half-life.

The value t is calculated as the time difference between the measurement and reference times and is taken as negatively signed if the measurement time is before the reference time.

VII.6.5. Presentation of results

Calculate and record the activity of the sample and its uncertainty, and confirm that it is within the requirements of the request form.

VII.6.6. Uncertainty estimation

Uncertainties must be estimated in accordance with Ref. [13].

VII.7. CRITERIA FOR APPROVAL/REJECTION

Table 4 details the performance checks to be carried out upon acceptance of the radionuclide activity calibrator and periodically thereafter, as well as after repair, together with the appropriate pass/fail criteria. These criteria will also form part of the technical specification of the calibrator. Procedures for carrying out the tests listed in Table 4 can be found in Section VII.8.

VII.8. PERFORMANCE CHECK PROCEDURES

VII.8.1. Check source response

Objective. Measurement of the check source response establishes the constancy of the system's response by examining the reproducibility in measuring a constant source over a long period of time, which is an indicator of the reproducibility of the electrometer and the integrity of the ionization chamber gas pressure. Ideally, at least one relatively long lived source in a reproducible geometry will be measured each day before the calibrator is used. Caesium-137 is a good option because of its long half-life and radionuclidic purity, although other radionuclides such as ^{57}Co , ^{60}Co or ^{226}Ra can be used. The procedure is as follows:

TABLE 4. PASS/FAIL ACCEPTANCE CRITERIA FOR PERFORMANCE CHECKS OF RADIONUCLIDE ACTIVITY CALIBRATORS

Test	Frequency of testing				Pass/fail criterion
	Upon acceptance/ after repair	At the start of each day of use	Monthly	Annually	
High voltage	✓	✓	✓	✓	±1%
Display	✓	✓	✓	✓	—
Zero adjustment	✓	✓	✓	✓	Within range of adjustment
Clock accuracy	✓	✓	✓	✓	±1 min
Background	✓	✓	✓	✓	±20% of current mean
Check source response (constancy)	✓	✓	✓	✓	±2% of reference value
Accuracy (over normal operating range)	✓			✓	Nuclide dependent; ±2% (SSRLs), ±5% (other laboratories)
Precision	✓		✓	✓	±1%
Relative responses	✓	✓	✓	✓	±2% of reference value
Subsidiary calibrations	✓			✓	±1% of reference value
Linearity	✓			✓	Within 2% (SSRLs) or 5% (other laboratories) of true value over operating range (compare with linear fit of data)
Geometry	✓				New factor must be determined for every change in geometry (SSRLs), or when effect of geometry is >5% (other laboratories)

- (1) Assay the check source using the appropriate radionuclide activity calibrator setting (e.g. use the ^{137}Cs setting to assay ^{137}Cs).
- (2) Measure background at the same setting and subtract from the activity indicated in step 1, or confirm the proper operation of the automatic background subtract circuit if it is used.
- (3) For each source used, record (e.g. plot, log) the activity measured, the model and serial numbers of the instrument, the identity of the radionuclide check source, the date of the check and the calibration setting used.
- (4) If the test result falls outside $\pm 2\%$ of the expected results, investigate the reason why and/or follow the non-conformance procedure.

VII.8.2. Relative responses test

Objective. This check is designed to ensure that the settings of the radionuclide activity calibrator for particular radionuclides have not changed. The procedure is essentially the same as that used for measuring the check source response.

- (1) Assay the check source using the radionuclide activity calibrator setting for one of the commonly used radionuclides.
- (2) Measure background at the same setting and subtract from the activity indicated in step 1, or confirm the proper operation of the automatic background subtract circuit if it is used.
- (3) For each source used, record (e.g. plot, log) the activity measured, the model and serial numbers of the instrument, the identity of the radionuclide check source, the date of the check and the calibration setting used.
- (4) Repeat the above procedure on all other settings for commonly used radionuclides. Record (e.g. plot, log) the results.
- (5) If any of the test results fall outside $\pm 2\%$ of the expected results, follow the non-conformance procedure.

VII.8.3. Linearity

Objective. This check confirms that, for an individual radionuclide, the same calibration setting can be used to indicate the correct activity over the range of use of that calibrator. It is important that the linearity of the radionuclide activity calibrator be ascertained over the range of its use between the maximum activity administered and 1 MBq. (Typically, the maximum activity for $^{99\text{m}}\text{Tc}$ will be about 150 GBq.) There are two possible methods, but consideration must be given to the potential radiation exposure of the operator when

conducting this test. In each of these tests, the half-life of ^{99m}Tc is taken as 6.0067 (10) hours [27].

VII.8.3.1. Time decay method

- (1) Take a syringe or vial containing a freshly eluted sample of ^{99m}Tc having at least the maximum activity normally encountered in daily practice and place it in the radionuclide activity calibrator. For radionuclide activity calibrators that have a range switch, select the range that would normally be used for the measurement and assay of the activity. Subtract background to obtain the net activity in MBq. Record the date, time to the nearest minute and net activity on the radionuclide activity calibrator linearity test form.
- (2) Repeat the assay at approximately two-hour intervals during the workday, remembering to switch the range where appropriate. Continue on subsequent days until the assayed activity is less than 1 MBq. (Where the calibrator output can be connected to a data capture device, the calibrator can be left to automatically assay and record over the whole measurement period, thus minimizing operator radiation exposure.)
- (3) Convert the time and date information recorded to hours elapsed since the first assay.
- (4) Determine the activity of the sample from a single reading obtained at an activity level between 20 and 40 MBq. Using the decay equation (Eq. (7)), calculate the expected activity at the times obtained in step 3. Alternatively, a best fit single exponential function of the data can be determined and used for decay correction calculations.
- (5) Record the measured activities, the calculated activities, the time elapsed between measurements, the model and serial numbers of the radionuclide activity calibrator, and the date(s) of the test.
- (6) If any of the test results fall outside $\pm 2\%$ of the expected results, follow the non-conformance procedure.

VII.8.3.2. Shield method

This test requires a set of shielding ‘sleeves’ of various thicknesses to test for linearity. These sleeves first need to be calibrated.

The user is encouraged to review the procedure for calibrating sleeves described below and compare it with the manufacturer’s instructions. Some sleeve manufacturers’ procedures indicate that various sleeves are to be nested to achieve a desired attenuation. The following procedure can be modified to allow for nesting of sleeves:

- (1) Begin the linearity test as described in the time decay method above. After making the first assay, the sleeves can be calibrated as follows. Steps 2 through 4 below must be completed within 6 min (i.e. approximately 1% of the decay of ^{99m}Tc).
- (2) Put the base and sleeve 1 in the radionuclide activity calibrator with the vial. Record the sleeve number and indicated activity.
- (3) Remove sleeve 1 and insert sleeve 2. Record the sleeve number and indicated activity.
- (4) Continue this process for all sleeves.
- (5) Complete steps 2 to 5 of the linearity time decay method test above.
- (6) From the data recorded in step 4 of the time decay method, find the decay time associated with the activity indicated with sleeve 1 in place. This is the 'equivalent decay time' for sleeve 1. Record that time with the data recorded in step 2.
- (7) Find the decay time associated with the activity indicated with sleeve 2 in place. This is the 'equivalent decay time' for sleeve 2. Record that time with the data recorded in the third step.
- (8) Continue this process for all sleeves.
- (9) Calculate the expected activity for each sleeve using the 'equivalent decay time' previously determined for each sleeve (step 6).
- (10) The table of sleeve numbers and equivalent decay times constitutes the calibration of the sleeve set.

The sleeve set may now be used to test radionuclide activity calibrators for linearity using the following procedure:

- (1) Assay the ^{99m}Tc syringe or vial in the radionuclide activity calibrator and subtract background to obtain the net activity. Record the net activity. Steps 2 through 4 below must be completed within 6 min.
- (2) Put the base and sleeve 1 in the radionuclide activity calibrator with the vial. Record the sleeve number and indicated activity.
- (3) Remove sleeve 1 and insert sleeve 2. Record the sleeve number and indicated activity.
- (4) Continue this process for all sleeves.
- (5) Record the measured activities, the calculated activities, the time elapsed between measurements, the model and serial numbers of the radionuclide activity calibrator, and the date(s) of the test.
- (6) If any of the test results fall outside $\pm 2\%$ of the expected results, follow the non-conformance procedure.

VII.8.4. Background

Objective. The ongoing monitoring of background is used as an indicator that the electronic noise is not deteriorating and that unexpected sources of radiation are not present. From the first month of background data obtained after acceptance, a mean value and its standard deviation are calculated to provide the benchmark.

- (1) Remove all radioactive sources from the radionuclide activity calibrator and its immediate vicinity. Assay background and record the result together with the model and serial numbers of the radionuclide activity calibrator, and the date(s) of the test.
- (2) If the measured background value falls outside three standard deviations from the mean background value determined at acceptance, follow the non-conformance procedure.

VII.8.5. Precision

Objective. This check is to confirm that the random uncertainty of a single measurement is primarily determined by the random nature of radioactive decay. A larger than expected value indicates the possible presence of another random source of uncertainty that had not been anticipated.

- (1) Insert the check source into the radionuclide activity calibrator and record ten sequential readings at 1-min intervals. Determine the mean and standard deviation.
- (2) Repeat this process nine times.
- (3) Perform decay correction calculations if appropriate (e.g. if >1% decay has taken place during the measurements).
- (4) Calculate the mean and standard deviation of the mean (SDOM) of all 100 measurements.
- (5) Determine the median value of the standard deviations (MSD) obtained in the first two steps and compare it with the SDOM obtained in step 4. The value of MSD/SDOM must be 10.
- (6) Repeat steps 1 to 4 using a long lived source that indicates an activity of approximately 1 MBq of radioactivity. (This can be achieved by suitably shielding the check source.)
- (7) If the value of MSD/SDOM is greater than 15, follow the non-conformance procedure.

VII.8.6. Accuracy

Objective. This check is to ensure that the activity values determined by the radionuclide activity calibrator are traceable to national or international standards of radioactivity within the indicated uncertainties. Sources to be used for this purpose must be traceable to an NMI and be provided with both a certificate to this effect and an uncertainty statement. At each confirmation of accuracy, at least two radionuclides, selected from the list of commonly assayed radionuclides, are to be used. An objective could be to include all commonly assayed radionuclides over a ten year cycle. Ideally, the sources used will be of the same volume and in the same container type as in routine assays. Source activities must be greater than 10 MBq.

- (1) Assay the calibrated reference source at the appropriate setting (i.e. use the ^{57}Co setting to assay ^{57}Co , taking account of volume and container characteristics), and then remove the source and measure the background. Subtract background from the indicated activity to obtain the net activity. Record the net activity.
- (2) Check that the measurement is within $\pm 5\%$ of the certified activity of the reference source, mathematically corrected for decay.
- (3) Repeat the procedure for any other calibrated reference sources possessed.
- (4) Record the model and serial numbers of the radionuclide activity calibrator, the model and serial numbers of each source used, the identity and activity of the radionuclide contained in the source, its volume and container characteristics, the date of the test and the results of the test.
- (5) If any of the test results fall outside $\pm 5\%$ of the expected results, follow the non-conformance procedure.

VII.8.7. Subsidiary calibrations

Objective. This check is to ensure that the calibration factors of the radionuclide activity calibrator for containers and volumes that are different from those used in the checking of accuracy are correct and that the container characteristics are still the same as originally specified.

- (1) Dispense aliquots from the same stock solution of a radionuclide into two containers. It is desirable that one of these be the same type of container as that for which the accuracy checks have been performed and that it contain the reference mass (or volume) for that calibration setting, and

that the other container be that for which the subsidiary calibration check is required and that it contain the relevant mass (or volume).

- (2) Assay both containers in the radionuclide activity calibrator, subtract background and decay correct to a common reference time. Calculate the activity concentration per unit mass (or volume) for each container.
- (3) Repeat the previous steps for at least one other radionuclide.
- (4) If any two of the activity concentrations calculated in the second step differ by more than 5%, follow the non-conformance procedure.

Appendix VIII

MEASUREMENT TRACEABILITY IN PRACTICE

According to the definition of traceability [6], three main points need to be considered when determining whether or not a measurement is traceable:

- (1) Traceability is relevant only in reference to a measurement result — not a laboratory, device, reference artefact or individual. Therefore, an entity cannot claim traceability for measurements of a particular radionuclide using a particular instrument solely on the basis of the fact that other radionuclides have been used to calibrate it.
- (2) Comparisons must be made directly and through an unbroken chain. This means that the item being measured must be directly compared with a standard in the same instrument or must be measured in an instrument for which a calibration factor has been directly determined through the use of a calibrated standard.
- (3) Traceability cannot be established in the absence of uncertainties. The concept of absolute traceability does not exist. Instead, a measurement result is said to be traceable within the limits of the uncertainties of both the measurand and the value of the standard against which the measurement is compared.

Example 1

It is common for secondary standard source suppliers to calibrate HPGe gamma ray detectors for a small set of energies using a series of calibrated sources that are traceable to an NMI. A calibration curve of efficiency versus energy is then developed that allows the efficiency at any other energy to be calculated. These efficiency values, along with the necessary decay scheme parameters, allow the activity of the radionuclide to be calculated from the counting data.

Manufacturers of many other types of measurement instrument, including radionuclide activity calibrators, use similar ‘sensitivity curves’ to calculate new calibration factors for new radionuclides. This is often done with calibrated ^{57}Co and ^{60}Co sources in order to cover as much of the practical energy range as possible. The decay data for the radionuclide are then used in conjunction with Monte Carlo calculations or simple interpolation along the sensitivity curve to determine the calibration figure.

In neither of these two cases can a valid claim of traceability be made. The reason is that a direct comparison between the standard and the counting source has not been made. The only cases for which a traceability claim would be valid would be measurements of the radionuclides actually used to perform the calibrations (e.g. ^{57}Co and ^{60}Co). Developing a calibration curve using standardized sources and applying it to a measurement of a radionuclide that was not used in the calibration does not provide a direct link to a primary standard.

Example 2

A hospital receives a dose vial containing 5 mL of a solution containing 370 MBq of a radionuclide from an isotope manufacturer that can demonstrate measurement traceability for that radionuclide to an NMI to within an uncertainty of 5%. The operator transfers 2 mL of the solution into a syringe and adds an additional 3 mL of saline solution to bring the volume to 5 mL. The syringe is placed in the hospital's radionuclide activity calibrator and, using the source supplier's radioactivity data, the operator changes the calibration setting on the calibrator until the display reads 148 MBq (two-fifths of the total activity originally in the vial). The resulting calibration setting is recorded and used for all measurements of the radionuclide in syringes in that calibrator.

Again, a claim of traceability would be invalid in this case. The primary reason is that a direct comparison cannot be made between the calibrated solution and the one prepared by the operator. Traceability can be achieved, however, if either the activity concentration (in units of $\text{MBq} \cdot \text{g}^{-1}$ or $\text{MBq} \cdot \text{mL}^{-1}$) or the total mass or volume of the solution is known, along with the total contained activity. With this information, one can accurately calculate the amount of transferred activity if the transfer is made either by mass or with an accurate volumetric dispenser. Moreover, it is possible to estimate the uncertainty of the activity value through knowledge of the uncertainties of the activity concentration and of the transfer.

REFERENCES

- [1] FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS, INTERNATIONAL ATOMIC ENERGY AGENCY, INTERNATIONAL LABOUR ORGANISATION, OECD NUCLEAR ENERGY AGENCY, PAN AMERICAN HEALTH ORGANIZATION, WORLD HEALTH ORGANIZATION, International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources, Safety Series No. 115, IAEA, Vienna (1996).
- [2] INTERNATIONAL ATOMIC ENERGY AGENCY, The Management System for Facilities and Activities, IAEA Safety Standards Series No. GS-R-3, IAEA, Vienna (2006).
- [3] INTERNATIONAL ATOMIC ENERGY AGENCY, Application of the Management System for Facilities and Activities, IAEA Safety Standards Series No. GS-G-3.1, IAEA, Vienna (2006).
- [4] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, General Requirements for the Competence of Testing and Calibration Laboratories, ISO/IEC 17025, 1st edn, ISO, Geneva (1999).
- [5] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Quality Management Systems – Requirements, ISO 9001:2000, ISO, Geneva (2000).
- [6] BUREAU INTERNATIONAL DES POIDS ET MESURES, International Vocabulary of Basic and General Terms in Metrology, 2nd edn, International Organization for Standardization, Geneva (1993).
- [7] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Proficiency Testing by Interlaboratory Comparisons – Part 1: Development and Operation of Proficiency Testing Schemes, ISO/IEC Guide 43-1:1997, 2nd edn, ISO, Geneva (1997).
- [8] WORLD HEALTH ORGANIZATION, Quality Assurance in Nuclear Medicine, WHO, Geneva (1982).
- [9] WORLD HEALTH ORGANIZATION, Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials, Vol. 1, WHO, Geneva (1997).
- [10] WORLD HEALTH ORGANIZATION, Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials, Vol. 2: Good Manufacturing Practices and Inspection, WHO, Geneva (1999).
- [11] EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES, European Pharmacopoeia, 4th edn, Council of Europe, Strasbourg (2002).
- [12] UNITED STATES PHARMACOPEIA, United States Pharmacopoeia 28/National Formulary 23, The United States Pharmacopoeia Convention, Inc., Rockville, MD (2005).
- [13] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Guide to the Expression of Uncertainty in Measurement, ISO, Geneva (1995).
- [14] LAMSON III, M., HOTTE, C.E., ICE, R.D., Practical generator kinetics, J. Nucl. Med. Technol. **4** (1976) 21–27.

- [15] PONTO, J.A., Expiration times for Tc-99m, *J. Nucl. Med. Technol.* **9** (1981) 40.
- [16] HAGGITH, J.W., The importance and required detection levels of radionuclide impurities – A medical physicist’s view, *Int. J. Nucl. Med. Biol.* **10** (1983) 85–89.
- [17] INTERNATIONAL ATOMIC ENERGY AGENCY, X-ray and Gamma-ray Standards for Detector Calibration, IAEA-TECDOC-619, IAEA, Vienna (1991).
- [18] DEBERTIN, K., HELMER, R.G., *Gamma- and X-ray Spectrometry with Semiconductor Detectors*, North Holland, Amsterdam (1988).
- [19] NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS, *A Handbook of Radioactivity Measurements Procedures*, 2nd edn, Rep. No. 58, NCRP, Bethesda, MD (1985).
- [20] LEO, W.R., *Techniques for Nuclear and Particle Physics Experiments: A How-to Approach*, 2nd rev. edn, Springer Verlag, New York (1994).
- [21] KNOLL, G.F., *Radiation Detection and Measurement*, 3rd edn, Wiley, New York (2000).
- [22] SCHRADER, H., *Activity Measurements with Ionization Chambers*, Monographie BIPM-4, Bureau international des poids et mesures, Sèvres (1997).
- [23] INTERNATIONAL ELECTROTECHNICAL COMMISSION, *Medical Electrical Equipment: Radionuclide Calibrators – Particular Methods for Describing Performance*, IEC 61303(1994-10), IEC, Geneva (1994).
- [24] INTERNATIONAL ELECTROTECHNICAL COMMISSION, *Calibration and Usage of Ionization Chamber Systems for Assay of Radionuclides*, IEC 61145(1992-05), IEC, Geneva (1992).
- [25] AMERICAN NATIONAL STANDARDS INSTITUTE, *Calibration and Usage of ‘Dose Calibrator’ Ionization Chambers for the Assay of Radionuclides*, ANSI Std N42.13-1986, ANSI, Washington, DC (1986).
- [26] INTERNATIONAL ATOMIC ENERGY AGENCY, *Applying Radiation Safety Standards in Nuclear Medicine*, Safety Reports Series No. 40, IAEA, Vienna (2005).
- [27] BÉ, M.M., et al., *Table of Radionuclides*, Monographie BIPM-5, Bureau international des poids et mesures, Sèvres (2004).

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