

NPL REPORT
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**A Review of UK Requirements for
a Measurement Infrastructure for
Radionuclides used in Positron
Emission Tomography**

S M Judge
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A Review of UK Requirements for a Measurement Infrastructure for Radionuclides used in Positron Emission Tomography

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ABSTRACT

Positron Emission Tomography (PET) is a medical imaging technique with many clinical and research applications. The number of PET Centres is set to expand in the UK over the next few years. As with other more established radiopharmaceuticals, the activities of any positron-labelled compounds administered to patients must be assayed to ensure the radiation dose the patient receives is as low as reasonably practicable, compatible with obtaining a good quality image. The National Physical Laboratory (NPL) already provides a UK measurement infrastructure enabling hospitals to achieve traceability to primary standards for β/γ -emitting radionuclides. Positron-emitting radionuclides, however, present additional measurement problems arising from geometric effects and the short half-lives of many of these radionuclides.

This review summarises the technical, regulatory and practical issues concerned with setting up a new infrastructure to ensure that measurements of PET radionuclides are accurate, consistent and traceable to national standards. The report includes feedback from visits to the user community. It concludes by recommending how the infrastructure should be established initially, using the existing NPL sample calibration service combined with a mobile service based on an NPL secondary standard ionisation chamber.

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1 Introduction

The use of Positron Emission Tomography (PET) is expanding in the UK for clinical and research applications. The technique involves the production of short-lived positron-emitting radionuclides using a cyclotron and then labelling suitable compounds with these radionuclides. These radiopharmaceuticals are injected into the patient and the carrier compound delivers the activity to the site of interest within the patient's body; a 3-D image is formed of the distribution of activity in the body, aiding diagnosis (for example, investigating the stage of cancer so the most effective treatment may be selected).

As with all radiopharmaceuticals used in nuclear medicine, the total activity (expressed in units of Becquerels (Bq)) of the radiopharmaceutical must be assayed before injection into the patient, to ensure that the patient receives the minimum radiation dose compatible with obtaining a useful image. The National Physical Laboratory (NPL) supports a technical infrastructure so that Nuclear Medicine Departments can ensure these measurements are accurate and consistent. The main method used has been the calibration of samples of radionuclides using NPL's secondary standard instruments which have previously been calibrated with primary standards of radioactivity. This method is difficult to implement for the short-lived radionuclides used in PET due to the time needed to transport samples.

The aim of this review was to establish the scope of the technical infrastructure needed to underpin the use of radionuclides for PET and to recommend how the infrastructure may be implemented. The report includes feedback from PET centres visited during 2004, and background technical and regulatory information in support of the recommendations.

2 *The role of the National Physical Laboratory*

The National Physical Laboratory (NPL) is the UK's national standards laboratory. The role of the laboratory is to provide world-class measurement standards and calibration facilities to enable organisations to make accurate and consistent measurements that are accepted nationally and internationally.

In the field of radionuclide metrology, NPL maintains and develops the UK primary standards of radioactivity. These primary standards are based on specialist equipment and procedures that enable the total activity of a sample of a radionuclide to be determined absolutely – no instrument calibration is needed.

To establish international acceptance for NPL primary standards, NPL compares its standards to those held at other National Measurement Institutes (NMIs). These comparisons are normally run under the auspices of the Bureau International des Poids et Mesures (BIPM) in Paris. The international acceptance of primary standards of radionuclides used in PET is summarised in the following section.

NPL offers customer services (based on secondary standard instruments) to enable users of radioactivity to compare their measurements to the primary standards. In the field of nuclear medicine, hospitals may send samples of radiopharmaceuticals to NPL for assay. NPL also organises proficiency testing exercises so that hospitals can demonstrate the accuracy of clinical measurements using 'blind' samples. These services form part of a technical infrastructure in the UK to ensure measurements of patient doses in nuclear medicine can be traced back to the primary standards of radioactivity, to ensure accuracy and consistency for patient safety and regulatory compliance.

3 *International acceptance of UK Primary Standards*

The procedure for gaining international acceptance of national primary standards has recently been formalised under the ‘Mutual Recognition Arrangement’ [1]. For radioactivity, the MRA has involved a series of comparisons of primary standards. These comparisons normally involve distributing samples taken from a bulk solution of the radionuclide to a number of national measurement institutes (NMI’s). Each institute determines the activity of their sample; the BIPM collates the results and publishes a report comparing the results from the different institutes. These reports are published on the BIPM web site and show the degree of equivalence between the institutes.

The short half lives of the radionuclides used in PET have precluded this approach (even for ^{18}F) due to the time needed to ship samples worldwide. However, it has proved possible to demonstrate the equivalence of national ^{18}F standards using a different method [2], as follows:

- 1) Each participating NMI used a specific type of ionisation chamber, developed at NPL (the NPL-CRC). The engineering tolerances on the components of this type of chamber are very tight so that each chamber manufactured is essentially identical to the master chamber held at NPL. Each chamber undergoes a rigorous quality control check at NPL during which its response (expressed in picoamperes per megabecquerel (pA MBq^{-1})) is compared to that of the master chamber for a number of radionuclides.
- 2) A sample of the positron-emitting radionuclide ^{68}Ga (in equilibrium with its parent, ^{68}Ge) was assayed on each chamber. These results were used to demonstrate that the response of the chamber to positron-emitting radionuclides had not changed since the quality control test.
- 3) Each NMI prepared a primary standard of ^{18}F and determined the response of its ionisation chamber (in pA MBq^{-1}).
- 4) The primary standards could then be compared by examination of measured instrument responses.

The results show excellent agreement between NMIs, supporting the claimed accuracy of the primary standard held at NPL and demonstrating equivalence to primary standards in other countries.

4 Regulations and guidance related to establishing the infrastructure

ARSAC Certification

Regulation 2 of the Medicines (Administration of Radioactive Substances) Regulations 1978 requires that any doctor or dentist who wishes to administer a radiopharmaceutical to a patient must hold a certificate issued by Health Ministers. Various changes to organisational aspects were covered under the Medicines (Administration of Radioactive Substances) Amendment Regulations 1995. These regulations were introduced to comply with the requirements of Article 5(a) of the European Council Directive 76/579/EURATOM and the later revisions 80/836/EURATOM and 84/847 EURATOM on basic safety standards.

The Administration of Radioactive Substances Advisory Committee (ARSAC) was set up to advise ministers on applications for certificates. The National Radiological Protection Board published “Notes for Guidance on the Clinical Administration of Radiopharmaceuticals and Use of Sealed Sources” in 1988 on behalf of ARSAC. Under this guidance, practitioners are expected to collaborate with physicists to assist the practitioner with procedures including the calibration of equipment and estimating tissue dose (paragraph 2.24). One principle of the guidance is that the activity administered to the patient must be the minimum consistent with acquiring adequate information (paragraph 3.2). The guidance goes on to specify ‘Diagnostic Reference Levels’ – the activity level of a radiopharmaceutical that is not expected to be exceeded when good and normal practice regarding diagnostic technical performance is applied. The Medical Exposure Directive 97/43/EURATOM requires Member States to promote the establishment and use of these Diagnostic Reference Values.

The Diagnostic Reference Levels for radionuclides used in PET depend on the compound and the clinical purpose. Typical activities are shown in Table 1.

Radionuclide	Typical activities for clinical applications (MBq)
^{11}C	400
^{13}N	550
^{15}O	2000
^{18}F	400

Table 1

Typical Diagnostic Reference Values used for Positron Emission Tomography (for guidance only in connection with instrument calibration – for clinical applications the reader should refer to the ARSAC publication).

During inspections for compliance with the terms of the ARSAC Certificate, it is normally expected that all administered activities are within 10% of the Diagnostic Reference Level (DRL). If activities are consistently greater than the DRL, further investigation and action may be taken even if the activities are within 10% of the DRL, as this could not be considered as optimisation [3].

POPUMET / IR(ME)R 2000

A second set of regulations concerned with protecting the patient is the Ionising Radiation (Protection of Persons Undergoing Medical Examination or Treatment) Regulations 1988 (the POPUMET regulations) and the Ionising Radiation (Protection of Patients) Regulations (Northern Ireland) 1988. These regulations are enforced under the Health and Safety at Work Act and also cover medical exposure to ionising radiation. The associated Guidance Notes state that:

‘The activity administered ... should be controlled and should be checked before administration. Equipment used for this purpose should be checked daily using a sealed test source and should be calibrated at quarterly intervals with standard sources which should be sealed sources unless these are not commercially available.’

These regulations were replaced in 2000 by the Ionising Radiation (Medical Exposure) Regulations which came into force to implement the European Directive 97/43/EURATOM. These regulations include the requirement for written procedures to ensure that quality assurance programmes are followed and procedures for assessing the activity administered. Other requirements are included on quality control, quality assurance and training (which should include instrument calibration).

IPSM Report No 65: Protocol for establishing and maintaining the calibration of medical radionuclide calibrators and their quality control

The IPSM Protocol [4] was written in order to give clear recommendations on how to perform the quality control of Radionuclide Calibrators. The main recommendations were:

- The calibration of the instrument should be traceable to a national primary standard
- Simulated sources should not be used
- The activity administered to the patient should be within 10% of the prescribed activity
- An accurate ‘Reference Instrument’ may be used to calibrate ‘Field Instruments’ – the ‘Field Instrument’ being intended for routine daily use, the ‘Reference Instrument’ being a Radionuclide Calibrator that has been

calibrated using secondary standard sources directly traceable to a national standards laboratory.

- For radionuclides used in PET, the recommended acceptable tolerances for these instruments are given in Table 2.

Parameter	Reference Instrument	Field Instrument
Precision – (standard deviation of the mean of 10 consecutive measurements)	0.5%	1%
Reproducibility (maximum deviation from the mean of repeated measurements at least 24 hours apart)	1%	2%
Linearity (maximum % deviation from true activity over the range required)	1%	5%
Agreement with secondary standard	2%	Not applicable
Agreement with tertiary standard (obtained using the reference instrument)	Not applicable	5%

Table 2

Summary of the recommended tolerances on Radionuclide Calibrators used to assay the activity of radionuclides used in PET (from IPSM Report 65).

The instrument should be tested at intervals given in Table 3.

Parameter	Frequency
Agreement with secondary / tertiary standard	Annually, using traceable reference standards for Reference Instruments and standards assayed on the Reference Instrument for Field Instruments
Precision / reproducibility	Annually
Subsidiary calibrations*	Acceptance testing
Checks on accuracy (stability of reading)	Daily (using a sealed check source)

Table 3

Intervals for testing Radionuclide Calibrators (from IPSM Guide 65). (*A subsidiary calibration is a calibration to establish the response of the instrument to radiopharmaceuticals in containers (for example, syringes) or volumes which are different from the containers or volumes used to calibrate the instrument.)

Regulations relating to Good Manufacturing Practice (GMP)

The government body responsible for ensuring the safety of pharmaceutical products in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA achieves this through a system of licensing, requiring compliance with Good Manufacturing Practice (GMP). GMP also imposes quality requirements on patient doses. The principles and guidelines of GMP are stated in an EC Directive (91/356/EEC).

Licensing of production

The Medicines for Human Use (Marketing Authorisations etc.) Regulations 1994 SI 3144 require that medicinal products are licensed before they can be marketed in the UK. Manufacturers must apply for a Marketing Authorisation and also comply with The Medicines (Standard Provisions for Licenses and Certificates) Regulations 1971 as amended by Amendment Regulations (SI 1972 No1226; SI 1983 No 1730; SI 1992 No 2846; SI1993 No 833; SI 1999 No 4; SI 2002 No236). These regulations include compliance with GMP.

Some patients may have clinical needs that are not covered by licensed products. The law allows the supply of unlicensed products subject to certain conditions (eg, no advertising of a service to supply such ‘specials’ is allowed). Manufacturers of ‘specials’ must hold a license issued by the MHRA and must also comply with the requirements of GMP. Since 1st May 2004, GMP also applies to the manufacture of products for clinical trials (The Clinical Trials Directive 2001/20/EC).

A license is not required (and hence GMP compliance is not compulsory) if the radiopharmaceutical is supplied as a dispensed medicine on a named patient basis; in this case, a qualified pharmacist takes responsibility for quality. This exemption may apply, for example, if a hospital’s cyclotron is used to provide radioactive material for administration to named patients within the hospital (but the conditions of the ARSAC certificate still apply).

Quality standards for patient doses

There are two issues under GMP related to the assay of activity in patient doses. First, all analytical measurements must be validated, where validation is the act of proving that the procedure, process, instrument or system actually leads to the expected result. The recommended procedures to be followed to validate an analytical technique are given in two publications from the ‘International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for human use’ (ICH):

- ICH Harmonised Tripartite Guideline ICH Q2B: Validation of Analytical Procedures: Methodology
- ICH Harmonised Tripartite Guideline ICH Q2A: Text of Validation of Analytical Procedures

Validation requires experimental data to demonstrate compliance, using well-characterised reference materials including data on their purity. These Guidelines are

similar to the IPSM Report 65, in that they require tests for parameters such as linearity and reproducibility.

The second issue under GMP is that the activity content of a dose of the radiopharmaceutical has to be within the range of activities stated on the Marketing Authorisation or the product specification. For some radiopharmaceuticals, the specification that the product is expected to meet is stated in the British Pharmacopoeia (BP) or in the equivalent European (Ph Eur) or US (USP) publications. This authoritative publication is the responsibility of the British Pharmacopoeia Commission (BPC) which was established in 1970 under section 4 of the Medicines Act 1968.

For Fludeoxyglucose [^{18}F] Injection (also known as ‘FDG’), the Ph Eur states in Monograph 1325:

- Measure the radioactivity using suitable counting equipment by comparison with a standardised fluorine-18 solution or using an instrument calibrated with the aid of such a solution. Standardised fluorine-18 solutions are available from laboratories recognised by the competent authority.

And the content must meet the following specification:

- The injection contains not less than 90.0 per cent and not more than 110.0 per cent of the declared fluorine-18 radioactivity at the date and time stated on the label.

The Ph Eur also gives general requirements for Radiopharmaceutical Preparations (Monograph 0125). This monograph re-iterates the requirement to identify and assay the radionuclides by comparing measurements with those from standardised preparations provided by laboratories recognised by the competent authority. The monograph also states that ‘it is essential for samples and standards to be measured under similar conditions’.

The monograph goes on to address the issue of radionuclidic purity of the radiopharmaceutical preparation: depending on the monograph for the radiopharmaceutical, the purity may be checked by γ -spectrometry or by measurements of the half life.

Medical Devices Directive

The Medical Devices Regulations 2002 SI2002 No 618 came into force on 13th June 2002 and implement EC Directive 93/42/EEC. These regulations specify essential requirements and controls on performance of all medical devices. Manufacturers are required to demonstrate compliance with these regulations before a device can be marketed in the UK.

A Radionuclide Calibrator is likely to be covered as a ‘Class 1 device with a measuring function’ under these regulations (the MHRA has not issued formal guidance on this at present). There is no specific requirement on measurement

accuracy under the regulations but the MHRA would expect the instrument to meet specification.

Conclusions – regulatory issues

- The regulations for the clinical use and the manufacture of radiopharmaceuticals require the activity of doses to be within 10% of the specified activity.
- This 10% tolerance implies that the calibration of the instruments used must have a lower uncertainty – certainly better than 5%
- The IPSM code of practice and GMP require that the calibration is established using a reference standard that is traceable to a national primary standard.

5 *Technical issues related to establishing the infrastructure*

It is useful to consider the response of an ionisation chamber to positron-emitting radionuclides to gain some insight into possible technical issues in establishing the measurement infrastructure.

There are two issues to address:

- 1) Variation in response of the instrument with container type and volume of solution, to indicate the amount of experimental work needed to confirm subsidiary calibrations (where a subsidiary calibration is a calibration to establish the response of the instrument to radiopharmaceuticals in containers (for example, syringes) or volumes which are different from the containers or volumes used to calibrate the instrument).
- 2) The variation in response for different positron emitters, to establish whether a calibration for a long-lived positron emitter may be a suitable analogue for a short-lived positron emitter.

Variation in response with container type and volume of solution

For a pure positron-emitting radionuclide, ionisation of the sensitive gas volume of the chamber may result from the following mechanisms, which are summarised in Table 4:

- 1) Direct detection of the positron

A high-energy positron may have sufficient energy to penetrate the container wall and the inner wall and ionise the gas directly. The probability of this type of event will be very sensitive to changes in wall thickness and composition, and solution volume.

2) Detection of Bremsstrahlung

Low energy X-rays will be emitted as the positron undergoes inelastic collisions in the surrounding materials. The magnitude of this effect will also be sensitive to changes in wall thickness and composition, and sample volume. However, the response of an ionisation chamber to Bremsstrahlung (and direct detection of the beta particles) is very low; results for the NPL Secondary Standard ionisation chamber show a response of 10.49 pA/MBq to F-18 but 0.03 pA/MBq for the pure beta emitter Sr-89 [6].

3) Detection of annihilation photons (511 keV)

The majority of the positrons emitted (95-100%) will lose kinetic energy through a series of inelastic collisions with the atoms in the surrounding materials. When the positrons reach the end of their range in matter, they will annihilate with an atomic electron resulting in the emission of two 511 keV photons. These photons pass readily through the walls of the container and the chamber and ionise the chamber gas.

Measurements with other radionuclides that have γ -emissions of a similar energy have shown that the response of the chamber does not depend strongly on container type or solution volume ([6],[7]). However, the point of origin of γ -emissions arising from the decay of such radionuclides is always within the solution, whereas the 511 keV photons resulting from positron annihilation are emitted at the end of the range of the positrons – the annihilation may take place in the wall of the container, in the closure, in the solution or in the walls of the chamber itself. The response of the instrument may be more dependent on the volume of solution and container than results for an equivalent γ -emitter suggest – no experimental data are available for this. Differences may be high for very small volumes as the majority of positrons will annihilate in the container and closure, rather than in the solution itself.

4) Detection of photons from annihilation in flight

A small percentage of positrons annihilate with atomic electrons before reaching the end of their range. This process results in the emission of two or three photons over a range of energy – these photons may then be detected in the chamber. The probability of this type of event increases with increasing positron energy and is of the order of 3% for a 1MeV positron depending on the material. Again, it is likely that the instrument response will depend on the volume of solution and the container.

Mechanism	Approximate magnitude of the response of the ionisation chamber (normalised to 100% for 511 keV photons)	Dependence on container type / solution volume
Direct detection of positrons	0-1%	High
Bremsstrahlung	0-1%	High
511 keV photons	100%	Typically <1% for small variations in volume for gamma-emitting radionuclides with similar energy photons. No data for small volumes or for positron emitting radionuclides.
Annihilation in flight	0-5%	No data available but 1-2% reasonable.

Table 4

Summary of the different physical mechanisms by which an ionisation chamber (Radionuclide Calibrator) responds to positron emission.

The conclusions that can be drawn are that the ionisation chamber should be calibrated using standards in the same container with the same volume as the samples to be measured, and that corrections should not be based on results from previous studies with γ -emitting radionuclides, particularly if small volumes of solution are to be assayed.

Variation of response with positron energy

The response of a typical ionisation chamber to positron emitters of different energy may not be identical due to:

- 1) Different spatial distribution of the production of 511 keV photons, due to the different range
- 2) Increase in probability of positron annihilation in flight with energy

The decay schemes of typical positron emitters used for PET are summarised in table 5.

Radionuclide	End-point energy (keV)	Intensity (%)	Notes
^{18}F	633.5	96.86	
^{11}C	960.5	99.75	
^{15}O	1735.0	99.885	
^{13}N	1198.45	99.818	
^{68}Ga	1899.1 821.7	87.94 1.2	Accompanying γ -emissions
^{64}Cu	653.1	17.86	

Table 5

Nuclear decay data of positron-emitters (taken from [9]).

The end-point energy of the main positron branches ranges from 633 keV to 1900 keV. The corresponding range of the positrons in water is from approximately 2mm to 9mm so the spatial distribution of the annihilation radiation could be significantly different – formed largely in the solution for low energy positrons and in the closure, vial wall or other surrounding materials for high-energy positrons.

The probability of annihilation in flight also varies with positron energy and absorbing material (3% at 1 MeV, 6 % at 2 MeV).

There are little experimental data available to confirm the order of magnitude of these effects. The response of an ionisation chamber to ^{18}F , ^{11}C and ^{68}Ga has been compared [4]. Good agreement was found between ^{18}F and ^{11}C (the response was found to be 5.42 pA per 106 511 photons for ^{18}F and 5.45 pA for ^{11}C , in agreement within the measurement uncertainties). However, a 3 % discrepancy was observed for the higher energy emitter ^{68}Ga when the response from γ -photons was subtracted. The reason for this discrepancy has not been established.

Taking these factors into consideration, it is recommended that the ionisation chambers are calibrated with the radionuclide of interest; longer-lived radionuclides such as ^{68}Ga (in equilibrium with ^{68}Ge) give similar responses (within a few %) and would be useful as check sources but are not recommended if the overall aim is an accuracy better than 5% to meet the regulatory requirements.

6 *Practical issues in establishing the infrastructure*

This section is a summary of feedback from visits to eight PET Centres and one manufacturer from February to August 2004. This is about 75 % of the PET Centres operating at present in the UK and is therefore a representative sample.

The aim of the visits was to discuss the practicality of setting up a measurement infrastructure for PET radionuclides.

UK P.E.T. Centres

There are 11 specialist PET Centres in the UK at present (see table 6).

Centre	Address	Main application
Wolfson Brain Imaging Centre	Addenbrooke's Hospital	Research
Paul Strickland Scanner Centre	Mount Vernon Hospital Northwood	Clinical
The Manchester PET Centre	Christie Hospital NHS Trust, Manchester	Clinical
Northern Ireland PET Institute	Royal Victoria Hospital, Belfast	Not known
John Mallard Centre	Aberdeen Royal Infirmary	Research
The Clinical PET Centre	Guys' and St Thomas' Hospital, London	Clinical – oncology
Hammersmith Imanet	Hammersmith	Research
The Institute of Nuclear Medicine	Middlesex Hospital, London	Clinical
Lister Healthcare	London PET Centre	Clinical
Wolfson Molecular Imaging Centre	Manchester	Not open yet.
The Institute of Cancer Research	Royal Marsden Hospital, Sutton	Clinical

Table 6

P.E.T. Centres in the UK

There are also at least 2 Mobile PET Centres; this number is expected to increase. Other hospitals use dual headed gamma cameras in place of PET cameras.

Radionuclides and activities used

The majority (80% or more) of doses of PET radionuclides administered in the UK are of ^{18}F (in the form of FDG) at the Diagnostic Reference Level (400 MBq). Other radionuclides reported as used regularly were:

- ^{11}C
- ^{15}O
- ^{13}N

Radionuclides that are used occasionally or are being considered for the future are:

- ^{68}Ga
- ^{64}Cu
- ^{62}Cu
- ^{62}Zn
- ^{124}I

Number of patients

The number of patients examined per year depended on the type of centre. Research units see between 100 and 500, whereas a clinical unit would see 1000-2000 (in one case, this number is expected to increase to 4000).

Based on available data, the total number of patients per year undergoing diagnostic procedures with PET is greater than 10000 and this number is expected to increase significantly over the next few years.

Containers

The radiopharmaceuticals are assayed in a variety of containers such as:

- Abbott vials (several sizes)
- Adelphi vials
- Syringes

Volume of solution assayed

The volume of solution assayed in vials varied from a few microlitres to 15ml. The volume drawn up into syringes ranged from 0.1 ml to 2 ml of solution.

Current approach to the calibration of instrumentation

The approach taken to calibrate Radionuclide Calibrators varied from centre to centre. Some units broadly followed the Code of Practice in IPSM Report No. 65, arranged regular calibration exercises using NPL reference sources of F-18 and applied corrections for different container types. Other units used NPL reference sources but applied no correction for container type and assumed the instrument response was independent of container and volume. Other centres had not calibrated the instrument and relied on data from the calibrator manufacturer.

Requested accuracy of calibration

Most centres aim to calibrate the ionisation chambers with an accuracy of between 2 and 5 %.

Use made of activity data

The main applications of measurements of the activity of the radionuclides were:

- 1) To demonstrate that the doses administered to patients were within 10% of the Diagnostic Reference Level, for compliance with the ARSAC Certificate
- 2) To report Standard Uptake Values
- 3) In the case of off-site cyclotrons, to check that the activity supplied by the manufacturer was within specification

Distribution

Shipment of radioactive materials was raised as an issue. Some hospitals distribute doses of FDG to other hospitals in the region and had members of staff certificated to sign transport documentation (by road). Other hospitals use FDG in-house only and had no system in place to ship samples.

7 Options for the infrastructure

There are essentially four different mechanisms that can be used to establish traceability (i.e. evidence that the measurement can be linked by an unbroken chain of comparisons to the UK primary standard). These four mechanisms are:

1 Calibration of a sample of the radionuclide at NPL

The instrument may be calibrated by assaying a sample of the radionuclide on the Radionuclide Calibrator, despatching it to NPL for certification and comparing the measured result to the NPL value. The half life must be long enough for shipping and a qualified person is needed to sign despatch documentation.

2 Calibration using a reference material from NPL or a traceable supplier

This is the inverse of method (1) – a certificated solution is received, dispensed to the appropriate container using a calibrated balance or pipette, and assayed on the instrument.

3 Using a transfer instrument

An instrument is despatched to NPL for calibration and certification on-site at NPL. This has the advantage that no despatch of radioactive materials is involved but benchmarking tests are needed before despatch and on receipt, to check that the calibration has not changed in transit. In addition, the environmental conditions in the clinical setting may not match the calibration environment (eg, proximity to other materials).

4 Using a secondary standard instrument

A secondary standard instrument such as the NPL-CRC Secondary Standard ionisation chamber has been designed with very tight engineering tolerances to match a master chamber held at NPL. Any calibration factors derived for the NPL master chamber may also be applied to the secondary standard chamber; an accuracy of better than 2% is specified. A regular stability test programme is needed to check the long term stability of the instrument.

Apart from the traceability issue, there are other aspects to the infrastructure for consideration:

1 Laboratory proficiency test exercises

These exercises may be used as an independent verification of the accuracy of measurement. NPL distributes blind samples of a radionuclide which are then assayed

and the results returned to NPL. The results may then be compared to the certificated values.

2 Measurement Good Practice Guides

Good Practice Guides are guidance on instrument calibration and validation, normally written by a writing group drawn from the user community with support from NPL.

3 User Forums

A User Forum is a forum facilitated by NPL to discuss technical problems in a particular field of measurement.

8 *Discussion and recommendations*

Radionuclides needed

As most of the patient doses in the UK arise from ^{18}F in FDG, it is recommended that traceability for this radionuclide be established in the first instance. From section 3, it is apparent that a longer lived analogue such as $^{68}\text{Ge}/^{68}\text{Ga}$ would not be suitable for technical reasons. There would also be no direct evidence to demonstrate traceability to Inspectors.

Accuracy required from the infrastructure

The feedback from the PET Departments visited was that a measurement tolerance of 10% was acceptable (ie, the administered dose should be within 10% of the prescribed dose). This is in agreement with regulatory requirements of the ARSAC licence and cGMP, and with IPSM Report No. 65.

This implies that the Radionuclide Calibrators should be calibrated such that the agreement with a secondary standard is better than 2%. This would result in an overall uncertainty of around 5% for subsidiary calibrations for other containers (such as syringes) and volumes.

This accuracy requirement means that there should be very few steps between the primary radioactivity standards and the assay of patient doses.

Dissemination of standards

The preferred method by the users to disseminate standards was for NPL to distribute samples of known activity to be used to check the calibration of instruments. The main reasons for this were:

- 1 Some PET centres did not have the infrastructure to despatch radioactivity to NPL for assay.
- 2 If the Certificate of Calibration was available at the time of delivery of the sample, the response factor for the ionisation chamber could be re-set and then checked immediately.
- 3 The sample could be dispensed to other containers and volumes for subsidiary calibrations.

The disadvantage of this system is that very high activities of ^{18}F would have to be dispensed at NPL, to allow for radioactive decay during transport. This would involve investment in a shielded enclosure (approximately £60k for an isolator plus the installation of extract ducts). The enclosure would be used infrequently, as once an initial calibration using ^{18}F was completed, the calibration could be maintained through the distribution of ^{68}Ge -samples. As modifications to the building and to the Environment Agency (EA) licence held by NPL would be needed, there would be a long delay before the service could be started.

9 Summary of recommendations

Stage 1

The first stage in establishing the infrastructure for the measurements of radionuclides used in PET should concentrate on ^{18}F .

Support from the PET Community and the commercial manufacturers should be sought to ensure that measurements are consistent, to reduce the risk of discrepancies in measurements between suppliers and users.

Two options should be offered:

- 1 For departments with the facility to despatch samples: NPL should maintain (and actively promote) a cost-effective service to assay samples. Alternatively, a local NPL-CRC Secondary Standard Calibration may be used if this is more convenient.
- 2 For departments with no facility to despatch samples: A service should be established for NPL staff to visit those departments, with an NPL Secondary Standard Calibrator. The Calibrator would be checked on arrival using a source of ^{68}Ge supplied by NPL and used to assay samples on-site. NPL staff would also advise on procedures for subsidiary calibrations.

Once calibrated using ^{18}F , the calibration should be checked annually using a sample of ^{68}Ge supplied by NPL.

Stage 2

- 1 NPL should seek the support of a supplier of ^{18}F to establish a regular proficiency testing programme for ^{18}F measurements.
- 2 The technical procedures used for dispensing the F-18 should be audited by NPL staff.
- 3 Traceability of the supplier should be established through a programme of regular comparisons.

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