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Comparison of ^{90}Y and ^{177}Lu measurement capability in UK and European hospitals

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HIGHLIGHTS

- ^{90}Y and ^{177}Lu measurement accuracy in UK and European hospitals is presented.
- 40% of participants are able to measure ^{90}Y to within 5%.
- 81% of participants are able to measure ^{177}Lu to within 5%.
- Geometry dependence is identified in radionuclide calibrator measurements of ^{90}Y.

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ABSTRACT

Comparison exercises involving ^{90}Y and ^{177}Lu were performed during 2009 and 2012, respectively, to assess the measurement capability of hospitals in the UK and Europe. The results from the measurement of a typical liquid solution of ^{90}Y show that only 40% of participants could measure the solution to within 5% of the certificated value and that a significant −6% bias was present due to the use of non-standard geometries for the calibration of equipment. The results from the measurement of a standard liquid solution of ^{177}Lu show that 81% of participants could measure to within 5% of the certificated value and in fact 65% of these results were within 2% of the certificated value, showing administered activities can be far more accurately measured for ^{177}Lu than for ^{90}Y and that ^{177}Lu has a far smaller geometry dependence. These studies were performed to identify specific measurement issues in the user community and to identify areas where future research should be focused. In addition to this the work allows the participants to adjust measurement practice and identify key measurement issues.

1. Introduction

^{90}Y has enjoyed something of a renaissance in popularity in recent years due to the increased use of novel chemical media such as microspheres and the labelling of this radionuclide to DOTA-TOC and DOTA-TATE agents to treat metastatic neuroendocrine tumours. ^{90}Y decays by virtually 100% β emission to the ground state of ^{90}Zr with a half-life of 2.6684 (13) days and maximum beta energy of 2279.8 (17) keV (DDEP, 2013). Due to internal pair production within ^{90}Zr, positrons are also emitted with an abundance of 31.86 (47) $\times 10^{-6}$ (Selwyn et al., 2007) which allows either PET imaging or bremsstrahlung imaging using SPECT or planar cameras. This can be used to localise the activity and subsequent dose distribution once administered to a patient. Due to the low emission probability of the positrons and the difficulty of imaging bremsstrahlung quantitatively, ^{90}Y would not be considered ideal from an imaging perspective. However due to its beta energy, short half-life, and chemical properties it has proven highly effective in the treatment of liver tumours, neuroendocrine cancers, and rheumatoid arthritis (through knee synovectomy) without causing excessive dose to surrounding healthy tissue (Torres et al., 2009; Goffredo et al., 2011).

^{177}Lu has recently undergone clinical trials as a surrogate for ^{90}Y in the treatment of neuroendocrine tumours. ^{177}Lu decays by 79.3 (5) % β emission directly to the ground state of ^{177}Hf and a further 20.7% β emission to three excited levels of ^{177}Hf with subsequent gamma cascades to the ground state (DDEP, 2013). ^{177}Lu has a half-life of 6.647 (4) days and a maximum beta energy of 498.3 (8) keV (DDEP, 2013) and this lends ^{177}Lu analogues to be favourable for use in radionuclide therapy in terms of reduced dose to surrounding healthy tissue whilst the primary gamma emissions at 112.9498 (4) keV and 208.3662 (4) keV (DDEP, 2013) are highly suited to imaging by planar or SPECT gamma camera techniques.

In Europe, prior to injection all radionuclides must be assayed to ensure administered doses are consistent with the planned

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therapeutic or diagnostic purpose of the exposure (Euratom, 1997). In External Beam Radiotherapy (EBRT) it is expected that the uncertainty on administered doses to target volumes will be known to within ±5% (TG21, 1983; TG51, 1999) and since the administered activity in a nuclear medicine therapy context is used to determine whole body dose, it stands to reason that this value should be known to an equal amount of accuracy. This is typically done by measurement in a radionuclide (dose) calibrator which consists of a high-pressure re-entrant ionisation chamber connected to an electrometer and user interface system allowing conversion of measured current into activity. These devices are optimised for measuring medium to high energy gamma emitters and use calibration factors, commonly referred to as dial settings, to convert current into activity. These factors are highly geometry dependant, particularly for isotopes which generate a large proportion of overall response from low energy photons or bremsstrahlung components caused by electron emissions. This manuscript details the results from two comparison exercises, performed in 2009 and 2012, respectively, in order to determine the accuracy with which ^{90}Y and ^{177}Lu is measured in the UK and Europe. These comparisons were initiated following discussions and consultation with members of the NPL Radionuclide Calibrator User Forum (RCUF) (NPL, 2013) and were open to any interested participant. The members of the RCUF represent a large proportion of the UK nuclear medicine community.

1.1. Preparation of sources

Both ^{90}Y and ^{177}Lu were supplied on behalf of NPL by Perkin-Elmer Inc. The solutions were prepared as a bulk stock from which nominal 4 ml aliquots were dispensed into 10 ml Type 1+ coated Schott© vials. The vials were measured at Perkin-Elmer using an in-house calibrator before dispatch to the participants to ensure consistency between samples. Perkin-Elmer is registered under ISO 9001:2008 (ISO, 2008) and both the ^{90}Y and ^{177}Lu groups operate consistently with Good Manufacturing Practice (GMP) for pharmaceuticals. The yttrium solution was subdivided into 33 individual samples with approximately 500 MBq total activity in each vial upon delivery to the participants. Six vials were sent to NPL for standardisation and homogeneity confirmation, the subset was chosen to represent 20% of the overall sample size (with a minimum of four vials). The samples were supplied as a radioactive solution of ^{90}Y in a carrier solution comprising 10 mg ml^{-1} yttrium in 0.1 mol dm^{-3} nitric acid. The lutetium solution was subdivided into 20 individual samples with approximately 400 MBq total activity in each vial upon delivery to the participants of which four were sent to NPL (again, the subset was chosen to represent 20% of the overall sample size with a minimum of four vials). The samples were supplied as a radioactive solution of ^{177}Lu as lutetium chloride in an aqueous solution of 1 mol dm^{-3} hydrochloric acid.

1.2. Standardisation of ^{90}Y

The ^{90}Y solutions were dispensed into 2 ml and 5 ml ampoules as defined in BS 795:1983 (BSI, 1983) which were then assayed using a high-pressure re-entrant secondary standard ionisation chamber, previously calibrated for ^{90}Y using the efficiency tracing method described by Baerg et al. (1963). A mean of the activity concentrations measured was determined and the activity concentration was confirmed by liquid scintillation counting techniques. In order to determine the individual vial activities, the activity concentration of the stock solution was multiplied by the individual vial solution masses which were supplied by Perkin-Elmer and corrected for buoyancy using a correction factor of 1.001 (Picard, et al., 2008; Davidson, et al., 2004). The masses supplied were confirmed by comparison of masses removed from vials, and derived activities were compared with calibrated activities for the vials sent to NPL. No gamma emitting impurities were expected due to the production process used, however measurements were performed using a High-Purity Germanium Detector and the Minimum Detectable Activity (MDA) of ^{88}Y at the time of measurement indicates a maximum of 50 Bq/100 MBq of ^{90}Y could have been present. This level of impurity would have a negligible effect on the response of a typical radionuclide calibrator. The presence of pure beta emitting impurities was checked by repeat measurements on a liquid scintillation counter and it was determined that <3 Bq g^{-1} of ^{90}Sr was present at the reference time of the sources which was deemed to be insignificant. The solution was also measured on the NPL Triple to Double Coincidence Ratio (TDCR) measurement system (Johansson and Sephton, 2010) and submitted to the international reference system (SIR) (Ratel, 2007) held at the Bureau International et Poids de Measures (BIPM) in Paris.

1.3. Standardisation of ^{177}Lu

The ^{177}Lu solution was dispensed into 2 ml and 5 ml ampoules, as above, which were then assayed using a high-pressure re-entrant secondary standard ionisation chamber, previously calibrated for ^{177}Lu using the beta-gamma coincidence counting technique (Campion, 1958) in conjunction with the efficiency extrapolation technique (Baerg, 1973). As with the ^{90}Y, the activity concentration was determined as a mean of these results, and the vial activities calculated by the multiplication of this value by the corrected vial solution mass. The presence of gamma-ray emitting impurities was checked using high resolution gamma ray spectrometry and ^{177m}Lu was found to be present with an activity concentration of 11.4 (6) kBq g^{-1} (uncertainty shown is combined standard uncertainty given at the 95% confidence level) at the reference time (2012-09-03 12:00 UTC) which corresponds to an impurity level of 0.011%. The correction required for the measurement of a 10 ml Schott vial containing 4 ml of solution on the NPL Vinten 671 as a function of time are shown in Table 1 and as a function of percentage impurity level are shown in Table 2.

Table 1
^{177m}Lu impurity correction required when measuring ^{177}Lu on NPL Vinten 671 system as function of time.

Time	Percentage current correction
Reference time	−0.30
Reference time+1 day	−0.32
Reference time+2 days	−0.36
Reference time+3 days	−0.40
Reference time+4 days	−0.44
Reference time+5 days	−0.48
Reference time+6 days	−0.54

Table 2
Correction required on NPL Vinten 671 as function of % ^{177m}Lu present in a ^{177}Lu sample as 4 ml in 10 ml Schott vial.

% ^{177m}Lu present	% Correction required on Vinten 671
<0.001	Negligible
0.005	0.15
0.01	0.30
0.02	0.61
0.03	0.91
0.05	1.52
0.1	3.03
0.2	6.06