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Radioassay of Yttrium-90 Radiation Using the Radionuclide Dose Calibrator

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Yttrium-90 is used in radioimmunotherapy because of its favorable physical half-life and energetic pure beta emissions. However, it is often necessary to standardize ^{90}Y sources to establish a dose calibrator dial setting for accurate calibration of clinical doses of ^{90}Y preparations. **Methods:** A solution of $^{90}YCl_3$ containing 2.81 kBq/ml (by supplier's calibration) was prepared by serial dilution in 0.05 *M* HCl. Ten 100-μl aliquots of this solution were counted in a Packard liquid scintillation analyzer; the mean radioactivity in becquerels was determined and used to evaluate dial settings 48 × 10, 775 × 70 and 775 × 100 on a radionuclide dose calibrator for ^{90}Y measurements. The dose calibrator response was also studied on ^{90}Y sources at varying solution volumes in plastic and glass containers. **Results:** Calibrator readings of ^{90}Y sources in glass and plastic vials and plastic syringes were accurate at either dial setting 48 × 10 (commonly used by many ^{90}Y laboratories) or 775 × 70. Measurements of 1.15 and 3.03 GBq (31 and 82 mCi, respectively) calibrated ^{90}Y sources in either vial were −3.0 and +4.3%, respectively, at dial-setting 775 × 70 and −4.0 and +9.0% at 48 × 10. Yttrium-90 sources in plastic syringes gave higher readings than those in glass vials, therefore, requiring a container correction factor for accurate dose assay. Measurements of $^{90}YCl_3$ shipments from four suppliers over a 3-yr period demonstrated concurring calibration measurements at both 775 × 70 and 48 × 10 settings for shipments from all suppliers. The dose calibrator response to ^{90}Y radiation was linear within a 1–333 kBq range in a constant sample volume of 580 μl. **Conclusion:** This work demonstrates the validity of using the 48 × 10 dial-factor combination on the standard radionuclide dose calibrator for calibration of ^{90}Y radiopharmaceuticals.

Key Words: yttrium-90; dose calibrator; assay; liquid scintillation; linearity test

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Yttrium-90 has attracted much research attention in radioimmunotherapy because its 64-hr half-life and pure beta emissions are potentially useful for cancer therapy. Some of its unique advantages (*1–5*) include: availability of methods for attaching the radiometal to chelate-carrying proteins and antibodies; physical $T_{1/2}$ suited for tumor localization; long-range beta emissions (maximum energy 2.2 MeV) capable of delivering homogeneous radiation to heterogeneous tumors (range 8–100 mm for soft tissue-solid tumors, respectively); and its decay to a stable daughter with no additional toxicities.

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The Nuclear Regulatory Commission and agreement state agencies require that radiopharmaceutical injectables be calibrated to within ±10% of the prescribed dosage (*6,7*). The Capintec radionuclide dose calibrators (Pittsburgh, PA) that have been designed for gamma-emitting radionuclides have become recognized as providing a handy tool for measuring ^{90}Y radiopharmaceuticals using the readily-produced bremsstrahlung radiation. Consequently, it is common for most clinics and other laboratory users to hold the calibration specifications of ^{90}Y suppliers as a reference and relate their own measurements accordingly. Apart from the popular calibrator dial setting of 775 with multiplication factor of 100 (or 775 × 100 dial setting), many laboratories have found that calibrator dial setting of 48 multiplied by 10 will give the suppliers' calibrated activities and hence calibrate their final ^{90}Y drug products. However, some laboratories still use other settings. This prompted Coursey et al. (*7*) of the National Institute of Standards and Technology (NIST) to advise that ^{90}Y users standardize their ^{90}Y sources by liquid scintillation counting (LSC), then use the standard source to establish appropriate dial-factor settings for ^{90}Y dose calibration on their radionuclide dose calibrators.

To investigate variation in calibration of shipments of ^{90}Y from many suppliers, we used LSC to standardize a ^{90}Y test sample and establish the agreement of dose calibrator measurements at dial settings 48 × 10 and 775 multiplied by an appropriate factor. The multiplication factor at which measurements at dial 775 were in agreement was found to be 70 not 100. The effects of quantity of ^{90}Y radioactivity, volume of samples and type of containers were investigated on measurements at these dial settings.

MATERIALS AND METHODS

The ^{90}Y source was purchased from four manufacturers as a carrier-free $^{90}YCl_3$ solution in 0.05 *M* HCl. The source vial from all suppliers was glass (≤1 ml in capacity). One of the sources was standardized by LSC using a Tri-Carb 1500 liquid scintillation analyzer, while all the sources were assayed on a Capintec CRC-12 radionuclide dose calibrator. The plastic Eppendorf tube (1.5 ml), syringes (1 ml and 50 ml) and glass vial (30 ml) used in the calibrator response experiments were purchased from Biorad (Hercules, CA), Becton Dickinson (Rutherford, NJ) and Gensia (Irvine, CA), respectively.

Gamma Spectrometry

A strong (stock) solution was prepared from the commercial $^{90}YCl_3$ source that was standardized by LSC by diluting a 75-μl aliquot to 2 ml in 0.05 *M* HCl. Two 100-μl $^{90}YCl_3$ sources prepared from this stock solution, one containing 2.3 MBq and another containing 281 kBq (assuming supplier's calibration data) were assayed for the presence of any gamma-emitting radionuclidic impurity using the Canberra (Meriden, CT) Acc-2 Accuspec/A multichannel analyzer (MCA). The MCA system was energy calibrated over 100–1200 keV using the standard photopeaks from an NIST (Gaithersburg, MD) mixed-gamma standard reference material 4275C. The absence of any radionuclide contaminants in the ^{90}Y sample was verified by the absence of any unexpected photopeaks in the bremsstrahlung spectrum.

Liquid Scintillation Counting Studies

Using the above $^{90}YCl_3$ stock solution, a final test solution containing exactly 2.81 kBq/ml (by supplier's calibration) was prepared by serial dilution in 0.05 *M* HCl. Exactly 100 μl aliquot of this test solution (281 Bq $^{90}YCl_3$) was placed inside each of 10 LSC vials. The content in each LSC vial was diluted to 20 ml with Ready-solv HP/b high-performance premixed LSC cocktail for aqueous samples. The vials were counted for 10 min each on the Packard liquid scintillation counter. The following expression was used to calculate the total activity in Becquerels (Bq) of the ^{90}Y:

$$\text{Disintegrations per sec (Bq)} = \frac{\text{Counts in 100-}\mu\text{l sample} \times \text{100-}\mu\text{l}}{\text{Absolute counting efficiency}}. \quad \text{Eq. 1}$$

A counting efficiency of 100% is specified for the instrument for ^{90}Y counting if it gives >50% counting efficiency for tritium. When calibrated against a tritium standard, the instrument gave a counting efficiency of 70%. An absolute counting efficiency of 1.0 was thus accepted for ^{90}Y on the instrument:

$$\text{Disintegrations per sec (Bq)} = \text{Counts in 100-}\mu\text{l sample} \times 100\ \mu\text{l}. \quad \text{Eq. 2}$$

Dose Calibrator Response Studies

A dial-setting calibration was investigated by measuring the entire $^{90}YCl_3$ shipment as received from the manufacturer at the dose calibrator dial settings 775 and 48. A 500-μl aliquot was removed from the source vial and similarly measured. Actual activity values were obtained by multiplying readings at dial 775 with 100 and 70 or those at 48 with 10. At a dose calibrator setting, the response coefficient ($D_{(N)}$) for a radionuclide (N) is given as:

$$R_{(N)} = D_{(N)}\, A, \quad \text{Eq. 3}$$

where A is the activity of the radionuclide sample and $R_{(N)}$, the dose calibrator reading. The response coefficients for ^{90}Y were calculated and compared at dial settings 48 × 10, 775 × 100 and 775 × 70.

The variations of these measurements from suppliers' calibrations were expressed in percentage variation (% var) according to the equation:

$$\%\ \text{var} = \frac{(\text{Calibration-measurement}) \times 100}{\text{Calibration}}. \quad \text{Eq. 4}$$

Therefore, negative % var values represent overestimates while positive values represent underestimates. Over a 3-yr period, shipments of ^{90}Y from four different suppliers were evaluated at the two dose calibrator settings and converted to the activities values described above. The individual measurements were then compared to the respective calibrated activities as specified by the suppliers.

TABLE 1
Dose Calibrator Dial-Setting Study Using Measurements of Shipment at Check-in and of a 500-μl Aliquot

Sample	Supplier's calibration	Dial 775 ×100	Dial 775 ×70	Dial 48 ×10
Supply	3.05	4.14	2.90	2.78
D	—	1.36	1.03	0.92
% var	—	−36	4.9	8.9
Aliquot	1.15	1.70	1.19	1.11
D	—	1.48	1.03	0.97
% var	—	−48	−3.5	3.5

Measurements are in GBq and are compared with the supplier's calibrated activity decayed to the time of assay. The response coefficient ($D_{(N)}$) and percent variation (% var) from supplier's calibration are shown for each dial setting (N). The ^{90}Y containers were glass (1-ml) for the shipment and plastic Eppendorf tube (1.5-ml) for the aliquot test samples.

The dose calibrator response to ^{90}Y sources was studied by measuring an aliquot of known volume from the $^{90}YCl_3$ shipment at the 775 × 70 and 48 × 10 dial settings, at varying solution volumes in water inside plastic Eppendorf tubes (50 μl to 1500 μl), syringes (50 μl to 1000 μl for the 1-ml syringe and 50 μl to 55 ml for the 60-ml syringe) and glass vial (50 μl to 35 ml) containers. The glass vials are the type commonly used by nuclear medicine clinics for radiopharmaceutical dose formulation. The plastic syringes are typical of those used for dispensing doses of radiopharmaceutical injectables. The Eppendorf tubes are the type frequently used in many laboratories as reaction vials, storage vials for ^{90}Y radiopharmaceutical samples and in other in vitro experiments.

The linearity of the dose calibrator response to ^{90}Y radiation was investigated by measuring the activity of a fixed aliquot (333 kBq/580 μl) at dial factors 775 × 70 and 48 × 10 for 3 wk. Observed readings (Obs) were converted to initial activity values using the first measurement time as a reference point. The percentage variation (% var) of each initial activity from the mean was calculated using an expression similar to Equation 3. The linearity and geometry tests have been performed at these two dial settings because they gave the closest initial measurements to the suppliers' calibrations.

RESULTS

The results of the MCA experiment indicated absence of any gamma-emitting radionuclides in the ^{90}Y supply. Specific note was made that the photopeak at 480 keV corresponding to ^{90m}Y was not observed in the gamma spectrum of the sample.

The mean counts per min per 100 μl for the 10 LSC samples was 18866 ± 238. This translated to activity concentration of 314 Bq/100 μl in the test aliquot compared with 281 Bq/100 μl by supplier's calibration in the same aliquot. The response coefficients at 775 × 70 and 48 × 10 were both found to be very close to unity, compared to the coefficient calculated at the setting 775 × 100 which was about 1.5 (Table 1). Also, all measurements of shipment samples at settings 775 × 70 and 48 × 10 were within the official limits of ±10% (Table 1).

A collation of some ^{90}Y radioassays at check-in from four suppliers over a 3-yr period are shown in Table 2. The accuracy of measurements at 775 × 70 and 48 × 10 was corroborated by all the suppliers.

The results of the dose calibrator response to ^{90}Y in different containers and for increasing test sample volumes in water are summarized in Tables 3 and 4. The supplier's calibration was used as reference in each of these studies. Dose calibrator

TABLE 2
Capintec Dose Calibrator Measurements (MBq) of $^{90}YCl_3$ Sources as Received from Suppliers A, B, C and D

Supply	Source (μl)	Supplier calibration	Dial 775 × 70	% var	Dial 48 × 10	% var
1A	1992	6068	5772	+4.9	5550	+8.6
2A	Dry	925	962	−3.2	962	−3.2
1B	800	2294	2294	±0.0	2146	+6.1
2B	400	1184	1258	−6.8	1184	±0.0
3B	400	703	703	±0.0	666	+4.3
1C	009	333	407	−24.2	370	−12.1
2C	066	370	333	+10.8	333	+10.8
3C	155	1850	1887	−2.2	1776	+3.8
1D	030	2701	2979	−10.3	2834	+4.9
2D	030	2923	3182	−8.9	3045	−4.2
3D	060	2442	2712	−11.1	2505	−2.6

measurements were most accurate at either setting 775 × 70 or 48 × 10 at any solution volume for a ^{90}Y source contained inside the 1.5-ml plastic Eppendorf tube and at solution volumes ≥10 ml for a ^{90}Y source inside a 30-ml glass vial (Table 3). However, measurements were overestimated at these settings when the ^{90}Y was contained in plastic syringes (Table 4). In the plastic syringe, the use of either 775 × 70 or 48 × 10 requires an additional multiplication (container correction) factor of 1.1 to convert readings of ^{90}Y sources inside glass containers to those inside plastic syringes.

The dose calibrator responses to ^{90}Y at 775 × 70 and 48 × 10 settings were linear between the range 1–333 kBq studied, as all measurements were within the official limits of ±10% (Fig. 1).

DISCUSSION

The absence of any detectable gamma-emitting radionuclidic impurity in the ^{90}Y source implied that the radiation counted in the LSC experiments was due only to energy originating from the beta particles of ^{90}Y. The result of ^{90}Y standardization by LSC (314 Bq) varied by −11.7% from the supplier's calibration (281 Bq). Consequently, the supplier's calibration was used as reference in the dose calibrator dial setting studies relating to the effect of source geometry, type of container or linearity of calibrator response on measured dose activity.

TABLE 3
Capintec Dose Calibrator Measurements (MBq) of Yttrium in Increasing Solution volumes (i.e., geometry test) in Plastic Tube and Glass Vial

Plastic tube (1.5-ml)			Glass vial (30-ml)		
Sample (μl)	Dial 775 × 70	Dial 48 × 10	Sample (ml)	Dial 775 × 70	Dial 48 × 10
50	67	63	0.05	148	137
100	67	67	2.5	133	122
150	67	67	5.0	122	115
200	67	67	10.0	118	115
300	67	67	15.0	118	115
500	67	67	17.5	118	111
800	67	67	22.5	118	111
1000	67	67	27.5	118	111
1300	67	67	32.5	118	111
1500	67	67	35.0	118	111

The supplier's calibrated activities were calculated for the test aliquots and decay-corrected to measurement time. The aliquot activities calculated from supplier's calibration were 67 MBq and 115 MBq for the plastic tube and glass vial, respectively.

TABLE 4
Capintec Dose Calibrator Measurements (MBq) of Yttrium in Increasing Solution Volumes (i.e., geometry test) in Plastic Syringes

Plastic (1.5-ml)			Plastic syringe (60-ml)		
Sample (μl)	Dial 775 × 70	Dial 48 × 10	Sample (ml)	Dial 775 × 70	Dial 48 × 10
50	74	70	0.05	130	122
100	74	70	5.0	130	122
150	74	70	10.0	130	118
200	74	70	15.0	126	118
300	74	70	20.0	130	118
500	74	70	25.0	126	118
800	74	70	30.0	126	118
1000	74	70	40.0	126	118
1300	74	70	50.0	126	118
1500	74	70	55.0	126	118

The supplier's calibrated activities were calculated for the test aliquots and decay-corrected to measurement time. The aliquot activities calculated from supplier's calibration were 67 MBq and 111 MBq for the 1.5-ml and 60-ml plastic syringes, respectively.

All ^{90}Y measurements at dial-factor 775 × 100 were very high, usually with percent variation from supplier's calibration in excess of 35% (Table 1). This setting, that was previously used by some manufacturers and nuclear medicine laboratories, seems to have been abandoned by most workers (*7*). The inappropriateness of the use of dial 775 × 100 for ^{90}Y measurement was further indicated by the disparity found between the response coefficient value of about 1.5 at this

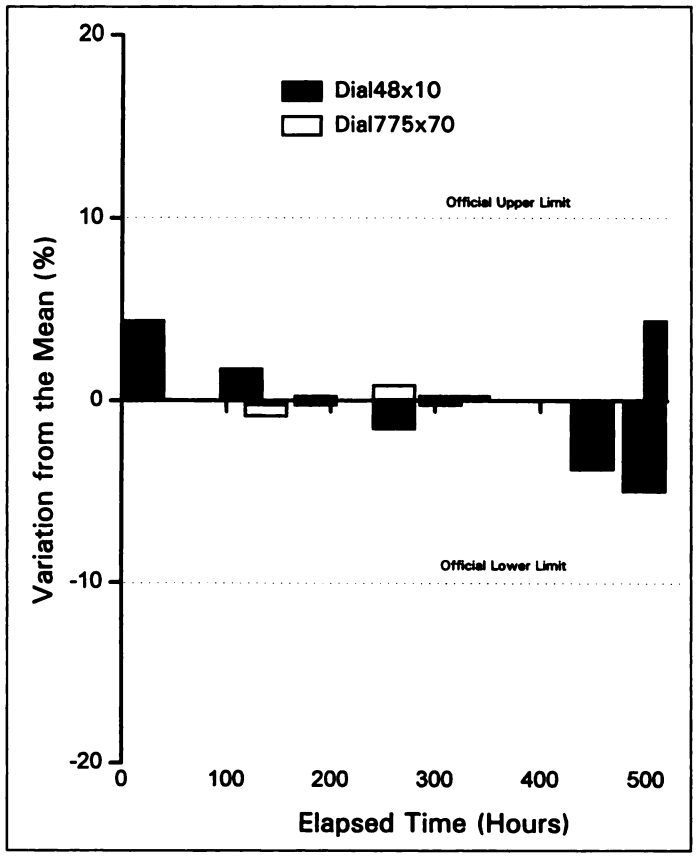

FIGURE 1. Capintec dose calibrator measurements (MBq) of ^{90}Y from a linearity experiment at the 775 × 70 and 48 × 10 dial settings. The percent variations from the mean measurement ranged from −3.2% to +4.4% for the dial 775 × 70 setting and −3.8% to +4.4% for the 48 × 10.

setting and 1.0 at both of 775 × 70 and 48 × 10. According to the calibrator manual, the response coefficient of the instrument to a unit activity ^{60}Co standard reference material is 1.0. Also, we observed that the percent variations in measurements (from the supplier's) for 1 and 3 GBq ^{90}Y sources were −4 and +9% at 48 × 10 compared with −3 and +5% at 775 × 70. Despite having the large (3 GBq/987 μl) and small (1 GBq/500 μl) ^{90}Y sources in different containers, measurements at combinations 775 × 70 and 48 × 10 were both within ± 10% of supplier's calibration. This shows that there is no pronounced container effect on accurate calibration of ^{90}Y sources when contained in these small glass vials (≤1 ml) and plastic Eppendorf tubes (≤1.5 ml).

Our results demonstrated the accuracy of ^{90}Y radioassays at 775 × 70 and 48 × 10 settings for ^{90}Y from all of the four suppliers (Table 2). The observed correlation between suppliers' calibration and dose calibrator measurements at the 775 × 70 and 48 × 10 settings was not found to depend on sample volumes since sample volumes in the shipments varied from 0 (dry product) to about 2 ml and all supplies were contained in similar glass vials (about 1 ml).

The difference in dose calibrations between the ^{90}Y source in the 1.5-ml plastic Eppendorf tube and that contained in a 30-ml glass vial (Table 3) is noteworthy. At all solution volumes in the Eppendorf tube, dose calibration measurements at 775 × 70 or 48 × 10 were the same as the calculated ^{90}Y activity based on the supplier's calibrations. However, in the glass vial, agreements were not achieved between the measurements at these settings and the calculated ^{90}Y activity from the supplier's calibration until the radioactive solution had been diluted to 10 ml.

The measurements of a ^{90}Y source contained in plastic syringes (Table 4), were uniform throughout all solution volumes except that those at the reliable setting combinations 775 × 70 and 48 × 10 overestimated the activity compared to the supplier's calibration. The maximum range of ^{90}Y in plastic is about 5.1 mm (*8*) compared to the thickness of the plastic syringe which is about 2 mm. Therefore, at lower solution volumes in plastic syringes, some ^{90}Y beta particles may be escaping the plastic, producing increased bremsstrahlung radiation in the metal lining of the dose calibrator leading to overestimation at the dose calibrator dial settings 775 × 70 and 48 × 10. This means that multiplication of measurements with a container correction factor may be necessary to convert the reading from a source inside a plastic syringe to the reading of the same source inside a glass container. Clinics using ^{90}Y need to decide which container (plastic syringe or glass vial) they prefer for their ^{90}Y radiopharmaceutical to assure dose calibration accuracy.

Measurements at both dose calibrator settings 775 × 70 and 48 × 10 were found to be linear between the range 1–333 kBq of source activity (Fig. 1). The percent variations from the mean measurement ranged from −3.2% to +4.4% for the dial 775 × 70 setting and −3.8% to +4.4% for the 48 × 10. This indicates a good performance for the dose calibrator at either setting since measurements were all within the official limits of ±10%.

CONCLUSION

Liquid scintillation counting has been used to corroborate the radioassay of ^{90}Y at the dose calibrator dial settings 48 × 10 and 775 × 70. Measurements of ^{90}Y at dose calibrator dial-factor 48 × 10 combination were within ±10% of most suppliers' calibrations. Similar studies have been reported for other radionuclides such as ^{89}Sr (*9*), ^{99m}Tc (*10*) ^{123}I in ^{124}I (*11,12*) and others (*13,14*).

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