

# Development of activity standard for $^{90}\text{Y}$ microspheres

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## Abstract

$^{90}\text{Y}$  microspheres are important therapeutic radiopharmaceuticals used in the treatment of liver cancer through a process known as selective internal radiation therapy. SIR-spheres<sup>®</sup> is a radiopharmaceutical product that is comprised of  $^{90}\text{Y}$  microspheres suspended in sterile, pyrogen-free water for injection into patients. It is necessary to establish for the SIR-spheres<sup>®</sup> production the capability of accurately measuring the activity of this product to a traceable national measurement standard. An activity standard for SIR-spheres<sup>®</sup> was developed from a standard for  $^{90}\text{Y}$  solution, employing a highly quantifiable chemical digestion process. Calibration factors for the manufacturer's ionisation chambers were determined for 1 and 5 ml of the SIR-spheres<sup>®</sup> product placed in Wheaton vials, for both 34% and 44% of  $^{90}\text{Y}$  microsphere concentration.

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## 1. Introduction

$^{90}\text{Y}$  microspheres are therapeutic radiopharmaceuticals used in the treatment of liver cancer (Houle et al., 1989). Following implantation via a catheter in the hepatic artery,  $^{90}\text{Y}$  microspheres become embolised in the microvasculature of liver cancer where they irradiate the tumour by a process known as Selective Internal Radiation Therapy (Stubbs and Cannan, 2002). This

results in the destruction of the tumour, while leaving most of the healthy liver tissue relatively intact.

SIR-spheres<sup>®</sup> is a radiopharmaceutical product comprised of  $^{90}\text{Y}$  microspheres suspended in sterile, pyrogen-free water for injection into patients. They are produced regularly by Australian Nuclear Science and Technology Organisation (ANSTO) Radiopharmaceuticals and Industrials (ARI) and exported by SIRTeX, an Australian Company, to the international market. In order to meet the traceability requirement of the end users and provide confidence in the product, there is a need to standardise the product and establish a traceable chain of radioactivity measurement.

In the SIR-spheres<sup>®</sup> product, the microspheres are non-biodegradable plastic beads, have a density of

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Fig. 1. 5 and 1 ml of SIR-spheres<sup>®</sup> in Wheaton vials.

1.0 g/ml and a diameter of approximately 35  $\mu\text{m}$ .  $^{90}\text{Y}$  used was the nuclear reactor-produced radionuclide. The concentration of the microspheres is approximately 40% and patient doses of SIR-spheres<sup>®</sup> product are usually prepared in a Wheaton vial by ARI with an activity of 3 GBq in a volume of 5 ml. The activity administered to each patient is approximately between 1 and 2.5 GBq for metastatic patients, and up to approximately 4.5 GBq for hepatocellular carcinoma patients. The activity measurement of each vial is performed in an ionisation chamber located in the ARI  $^{90}\text{Y}$  production area. The make and model of this ionisation chamber is unknown. The activity measured in this chamber is checked with a TPA ionisation chamber (Sharpe and Wade, 1951) and a Vinten ionisation chamber (NE Technology, 1991) located in the ARI Quality Control (QC) Section, using 1 ml SIR-spheres<sup>®</sup> sample dispensed from the same stock of SIR-spheres<sup>®</sup> as the product. In this paper these three chambers will be noted as the ARI production chambers, ARI QC TPA and ARI QC Vinten chambers, respectively. Fig. 1 shows 1 and 5 ml SIR-spheres<sup>®</sup> contained in Wheaton vials.

The aim of this work was to establish for the ARI SIR-spheres<sup>®</sup> manufacture and quality control process the capability to reliably measure the activity of SIR-spheres<sup>®</sup> with traceability to national measurement standards. This paper describes how the process was accomplished.

## 2. Method

$^{90}\text{Y}$  decays by pure beta emission to  $^{90}\text{Zr}$  with an end point energy of 2.28 MeV. The half-life of  $^{90}\text{Y}$  is  $64.053 \pm 0.020$  h (Kossert and Schrader, 2004). The absolute activity measurement of this high-energy pure  $\beta$  emitter has been performed using the CIEMAT/NIST method (Grau Malonda and Garcia-Torano, 1982; Coursey et al., 1986) of liquid scintillation efficiency tracing with  $^3\text{H}$  (Coursey et al., 1993; Kossert and

Schrader, 2004). The triple-to-double coincidence ratio (TDCR) method (Simpson and Meyer, 1994; Zimmerman and Ratel, 2005) and  $4\pi\beta$  high-pressure proportional counting system (Woods et al., 1996) were also used for the standardisation of  $^{90}\text{Y}$ .

In this work, primary and secondary standardisations were first performed on a  $^{90}\text{Y}$  solution. Through chemical digestion of the SIR-spheres<sup>®</sup>, a secondary standard factor for the  $^{90}\text{Y}$  solution was then converted into a secondary standard factor for the SIR-spheres<sup>®</sup>. Finally, ARI production chamber and ARI QC TPA and Vinten chambers were calibrated for the SIR-spheres<sup>®</sup>.

The ionisation chamber calibration factors were determined using samples with two different microsphere concentrations to examine the effect of microsphere concentration on the calibration factor.

Experimental uncertainties were evaluated in accordance with the ISO GUM (International Organisation for Standardisation, 1993) and are quoted here as standard uncertainties which have coverage factor  $k = 1$  providing a confidence level of 68% unless otherwise specified.

### 2.1. Primary and secondary standardisation of $^{90}\text{Y}$ solution

$^{90}\text{Y}$  in 0.1 M sulphuric acid solution was produced at ARI. The sulphuric acid was used to dissolve the active yttrium oxide powder. Two sample sets were prepared from this stock solution. One sample set with volume of 5 ml was used for primary standardisation at the National Institute of Standards and Technology (NIST) in USA using the CIEMAT/NIST method of liquid scintillation efficiency tracing with  $^3\text{H}$  to determine the absolute activity concentration (in MBq/g) of the stock solution. The other sample set with volumes of 1.5 and 5 ml was used to determine the current response (in pA/g) of the ANSTO Secondary Standard ionisation chamber. The volumes are nominal values. The exact mass of the solution was determined by weighing the vial together with the bung and cap before and after dispensing. The calibration factor (in pA/MBq) for the ionisation chamber was then calculated from the ratios of the results of the two sets of measurements.

The same procedure was carried out on another occasion, but this time the primary standardisation was performed at the Council for Scientific and Industrial Research–National Measurement Laboratory (CSIR-NML) in South Africa using the TDCR method. These two batches were unrelated in origin and prepared at the different times. On both occasions, the solutions were checked for photon-emitting impurities with a germanium detector. Confidence in the measurements made by NIST and the CSIR-NML was established through participation in an international comparison of activity

measurements of  $^{90}\text{Y}$  (Zimmerman and Ratel, 2005). Comparable results were obtained with those of the other participating laboratories, the results agreeing with the average value to better than 0.15% and within one standard deviation of the inter-comparison mean value.

The ANSTO Secondary Standard ionisation chamber is a TPA ionisation chamber. Volumes of 1.5 and 5 ml of  $^{90}\text{Y}$  solution in Wheaton vials were calibrated for the ionisation chamber using the following formula that includes the correction for photon emitting impurities:

$$C_{90\text{Y}} = \frac{I_s}{A_{90\text{Y}}} - \sum_{i=1}^n (R_i \times C_{i-\text{imp}}), \quad (1)$$

where  $C_{90\text{Y}}$  (pA/MBq) is ionisation chamber calibration factor for  $^{90}\text{Y}$ ,  $I_s$  (pA) is the sample ionisation current measured in the ionisation chamber and corrected for background current and instrument drift (using Ra-226 reference sources),  $A_{90\text{Y}}$  (MBq) is the  $^{90}\text{Y}$  activity of the sample,  $R_i$  is the activity ratio of impurity to  $^{90}\text{Y}$  and  $C_{i-\text{imp}}$  (pA/MBq) is the calibration factor for the impurity.

## 2.2. Deriving the calibration factor for 1 ml SIR-spheres<sup>®</sup> from the secondary standard for $^{90}\text{Y}$ solution

One milliliter SIR-spheres<sup>®</sup> samples with two different microsphere concentrations (34% and 44% in volume) were prepared in Wheaton vials at ARI. The SIR-spheres<sup>®</sup> stock was stirred for approximately 15 min, before dispensing was done, to ensure the

homogeneity. Two samples were prepared for each concentration. These samples were labelled  $^{90}\text{Y}$ -m-1 and  $^{90}\text{Y}$ -m-2 for the concentration of 34% and,  $^{90}\text{Y}$ -m-3 and  $^{90}\text{Y}$ -m-4 for 44%. They were checked for photon-emitting impurities with a germanium detector.

Fig. 2 illustrates the procedure for deriving the ionisation chamber calibration factor for 1 ml SIR-spheres<sup>®</sup> sample.

### 2.2.1. Ionisation current measurement of 1 ml SIR-spheres<sup>®</sup>

As shown in the Fig. 2, the 1 ml SIR-spheres<sup>®</sup> samples ( $^{90}\text{Y}$ -m-1,  $^{90}\text{Y}$ -m-2,  $^{90}\text{Y}$ -m-3 and  $^{90}\text{Y}$ -m-4) were first measured in the ANSTO Secondary Standard and ARI QC TPA and ARI QC Vinten chambers to obtain current responses. To eliminate the effect of movement of microspheres on the current measurement, the samples were allowed to completely settle with the microspheres resting at the bottom of the vial, before measurements were undertaken in the ionisation chambers, ensuring a reproducible geometry. It took about 15 min for complete settling after the cessation of the agitation.

### 2.2.2. Chemical digestion

The secondary standard developed for  $^{90}\text{Y}$  in solution form is not suitable for the determination of the activity of SIR-spheres<sup>®</sup> due to the different sensitivity (National Council on Radiation Protection and Measurements, 1985) of an ionisation chamber to  $^{90}\text{Y}$  in these two different forms. In order to transfer the secondary

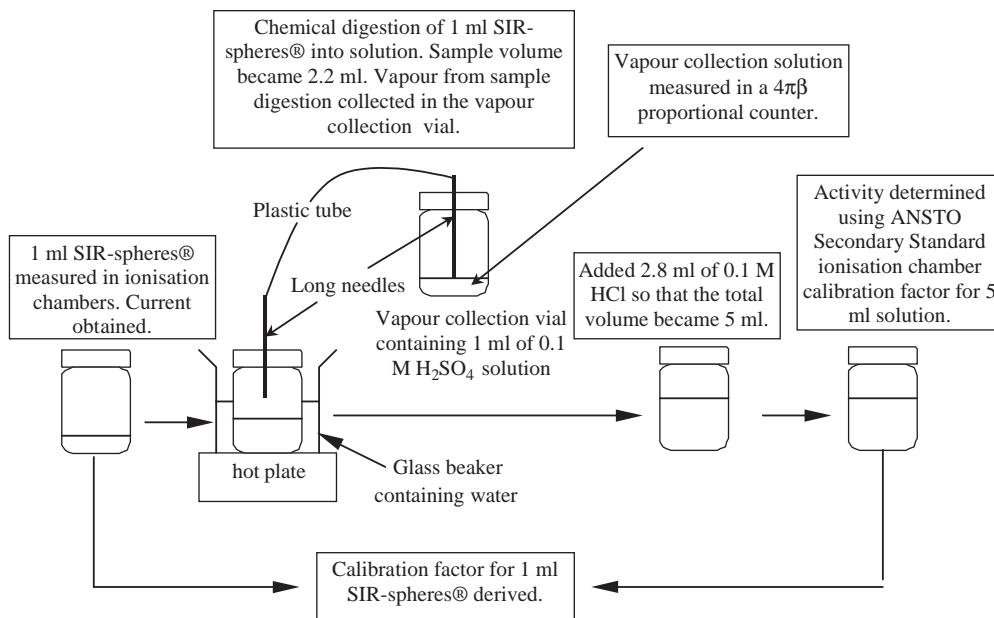


Fig. 2. Procedure for deriving the calibration factor for 1 ml SIR-spheres<sup>®</sup>.

standard factor for  $^{90}\text{Y}$  solution to the SIR-spheres<sup>®</sup>, a process of chemical digestion was employed.

As shown in the Fig. 2, after being measured in the various ionisation chambers, SIR-sphere<sup>®</sup> samples then underwent chemical digestion. The sample vial with reagents added in was placed inside a 50 ml glass beaker containing approximately 20 ml of water. The vials were crimp-sealed. A hotplate was used to heat the water to between 60 and 85 °C to increase the rate of digestion. The reaction of microspheres with the reagents caused vapours to be produced. A vial containing 0.5 ml of 0.1 M  $\text{H}_2\text{SO}_4$  solution was set up to collect the vapour from the sample digestion through a plastic tube. Both ends of the tube were connected to a long needle. One needle was plugged inside the sample vial, suspended above the solution. The other needle was plugged into the  $\text{H}_2\text{SO}_4$  solution in the vapour collection vial, so any  $^{90}\text{Y}$  atoms that were released could be dissolved. The collection of vapour also reduced pressure build-up in the closed vial due to heat and reaction. The activity of the solution in the vapour collection vial was measured in a  $4\pi\beta$  proportional counter. This activity (called activity loss), if significant, would be added to the sample activity. After the digestion, the sample volume increased to 2.2 ml as a result of the addition of chemical agents for digestion of the SIR-spheres<sup>®</sup>. The volume of each sample was then made up to 5 ml with the addition of 0.1 M HCl. Finally the digested SIR-spheres<sup>®</sup> were measured in the ANSTO Secondary Standard ionisation chamber and the activity determined using the calibration factors for a 5 ml solution. Further details of the digestion process cannot be disclosed for commercial reasons.

After chemical digestion, four 5 ml sample solutions for ionisation chamber measurements and four vapour collection solutions for quantification of activity loss during chemical digestion were produced from the original four samples  $^{90}\text{Y}$ -m-1,  $^{90}\text{Y}$ -m-2,  $^{90}\text{Y}$ -m-3 and  $^{90}\text{Y}$ -m-4.

The chemical digestion process described above was carried out with non-active SIR-spheres<sup>®</sup> samples before the active samples. The non-active digested SIR-spheres<sup>®</sup> were examined under a microscope with a magnification of  $\times 20$  to ensure that the digestion process was appropriate and the digestion was completed.

### 2.2.3. Measurement of activity lost in the chemical digestion

From each of the four vapour collection solutions, a  $4\pi$  counting source was produced by depositing known amount of aliquots onto a VYNS film (Wyllie, 1989). The VYNS counting sources were then measured in the  $4\pi\beta$  gas-flow proportional counter, the counting gas being argon containing 10% methane. With the beta channel main amplifier in its normal (not overloaded)

state, the beta particle counting efficiencies achieved previously were 97% for  $^{198}\text{Au}$  (maximum beta energy of 1372.5 keV) (Reinhard et al., 2003) and 96% for  $^{60}\text{Co}$  (maximum beta energy of 317.9 keV) (Mo et al., 2004). The  $^{90}\text{Y}$  beta emissions have a comparatively high maximum energy of 2283.9 keV. It is thus reasonable to assume the beta particle counting efficiencies for  $^{90}\text{Y}$  to be 98%. The uncertainty in the activity measurement due to this assumption was estimated to be less than 2%.

Non-extendable dead times of  $8.00 \pm 0.01 \mu\text{s}$  were measured. Each source was counted for ten intervals of 300 s duration. Counting data were collected on two subsequent days for each source. The observed count rates for each sample were corrected for background and dead time using Wyllie's equation (Wyllie, 1987).

### 2.2.4. Determination of calibration factor for 1 ml SIR-spheres<sup>®</sup>

After chemical digestion, a 1 ml SIR-spheres<sup>®</sup> sample became a 5 ml solution where activity was then able to be determined using the secondary standard calibration factor for the 5 ml solution. The calibration factor for 1 ml SIR-spheres<sup>®</sup> was calculated as a ratio of the ionisation current of a 1 ml SIR-spheres<sup>®</sup> sample before digestion to the total activity of the sample. The total activity includes the digested SIR-spheres<sup>®</sup> sample activity plus the activity loss during chemical digestion, if the loss is significant.

### 2.3. Determination of calibration factor for 5 ml SIR-spheres<sup>®</sup>

As described in the Introduction, patient doses of SIR-spheres<sup>®</sup> are prepared in a Wheaton vial in a volume of 5 ml. The activity of the patient dose is measured in the ARI production chamber. Therefore, it was necessary to calibrate this chamber for 5 ml SIR-spheres<sup>®</sup>. The calibration factors for 5 ml SIR-spheres<sup>®</sup> were also derived for the ANSTO Secondary Standard, ARI QC TPA and Vinten chambers. Due to the difficulties of completely digesting 5 ml SIR-spheres without adding high volumes of reagents and still keeping the sample volume measurable in an ionisation chamber, the calibration factors were derived from the secondary standard factor for 1 ml SIR-spheres<sup>®</sup>.

Two 1 ml and two 5 ml SIR-spheres<sup>®</sup> samples with microsphere concentration of approximately 43% (by volume) were prepared from the same stock at ARI. The samples were checked for photon-emitting impurities with a germanium detector.

Two 5 ml SIR-spheres<sup>®</sup> samples were measured in all the ionisation chambers so as to obtain the ionisation current. Two 1 ml SIR-spheres<sup>®</sup> samples were measured in the ANSTO Secondary Standard ionisation chamber in order to determine the activity concentration of the SIR-spheres<sup>®</sup> stock, from which the activities of the 5 ml

SIR-spheres<sup>®</sup> samples were calculated. The calibration factor for 5 ml SIR-spheres<sup>®</sup> was then determined by dividing the SIR-spheres<sup>®</sup> sample current by its activity. Due to practicality, the 5 ml samples were measured in the ARI production chamber immediately after dispensing and before the microspheres settled at the bottom. Five repeated measurements were made in 2 min.

### 3. Results and discussion

#### 3.1. Primary and secondary standardisation of <sup>90</sup>Y solution

The <sup>88</sup>Y impurity was detected in both batches of the primary standardisation solutions, with 0.00046% for the CIEMAT/NIST method batch and 0.00026% for the TDCR method batch. The TDCR measurement result was checked against the CSIR-NML ionisation chamber, for which a calibration figure had been obtained during the international intercomparison. Agreement to better than 1% was obtained, giving confidence in the measurements.

The response of the ionisation chamber to <sup>90</sup>Y was low since the chamber measured almost entirely low-energy bremsstrahlung produced by the interactions of the beta particles mainly with the solution and vial. <sup>88</sup>Y emits high-energy gamma rays in the range 484–3218 keV. The predominant photons emitted have energies of 898 and 1836 keV with emission probabilities of 94% and 99%, respectively. The calibration factor of <sup>88</sup>Y for the ANSTO Secondary Standard ionisation chamber is 65 pA/MBq which is nearly 300 times more than that of <sup>90</sup>Y. However, the content of <sup>88</sup>Y impurity was too low in respect of <sup>90</sup>Y activity to have a significant effect on the calibration factor.

The calibration factors for the ANSTO Secondary Standard ionisation chamber derived from the primary standardisations using Eq. (1) were 0.238 pA/MBq ± 0.83% for the 1.5 ml <sup>90</sup>Y solution and 0.218 pA/MBq ± 0.74% for the 5 ml <sup>90</sup>Y solution. The calibration factors decreased with increasing volume, in agreement with the experiments of Coursey et al. (1993).

#### 3.2. Determination of calibration factor for 1 and 5 ml SIR-spheres

The activity level for photon emission impurities found in samples <sup>90</sup>Y-m-1, <sup>90</sup>Y-m-2, <sup>90</sup>Y-m-3 and <sup>90</sup>Y-m-4 were below the detection limit of the germanium detector. The measured ionisation currents of these samples before digestion and their activities determined using the secondary standard factor for 5 ml solution are listed in Table 1. The uncertainty components for the ionisation currents and activities are given in Table 2.

The plastic tubes connecting two vials for the collection of vapour from digestion were examined by a surface contamination monitor and negligible count rate was observed. The activity loss for each 1 ml SIR-spheres<sup>®</sup> sample during chemical digestion is tabulated in Table 3.

From Table 3, it can be seen that the activity loss was less than 0.006% of the activity of the SIR-spheres<sup>®</sup> sample before digestion. Therefore, the activity loss was considered negligible. However, 0.006% was assigned as a B type uncertainty component (as shown in Table 2).

The calibration factors for 1 ml SIR-spheres<sup>®</sup> in a Wheaton vial for each ionisation chamber are listed in Table 4. The uncertainties are combined uncertainties of the components due to the ionisation currents and activities shown in Table 1.

There was no obvious change in the ionisation current for the first and last measurement for the same unsettled sample, measured in the ARI production ionisation chamber. It might be because of that the whole set of measurements were completed in 2 min that was not long enough for the microspheres to move greatly to affect the current. The calibration factors for 5 ml SIR-spheres<sup>®</sup> in a Wheaton vial for each ionisation chamber are listed in Table 5. Although 0.00006% of <sup>88</sup>Y impurity was detected in this batch, it was too low to make impurity corrections.

The factor for 5 ml SIR-spheres<sup>®</sup> derived in this way might result in a larger uncertainty because the SIR-spheres<sup>®</sup> stock might not be very homogeneous although the stirrer was used. This can be seen from the standard deviation, which was found to be 1%, of

Table 1  
Ionisation currents measured in various ionisation chambers and activities of 1 ml <sup>90</sup>Y SIR-spheres<sup>®</sup>

Sample	Ionisation current (pA) before chemical digestion			Activity (MBq) <sup>a</sup>
	ANSTO Secondary Standard	ARI TPA	ARI Vinten	
<sup>90</sup> Y-m-1	350.4 ± 0.88%	284.7 ± 1.7%	100.5 ± 1.6%	1452 ± 1.2%
<sup>90</sup> Y-m-2	349.1 ± 0.88%	284.1 ± 1.7%	100.8 ± 1.6%	1445 ± 1.2%
<sup>90</sup> Y-m-3	509.6 ± 0.88%	415.2 ± 1.7%	146.4 ± 1.6%	2108 ± 1.2%
<sup>90</sup> Y-m-4	507.9 ± 0.88%	414.6 ± 1.7%	147.0 ± 1.6%	2093 ± 1.2%

<sup>a</sup>The activity quoted in this table does not include the activity loss during chemical digestion.

Table 2  
Uncertainty components for the ionisation currents and activities of 1 ml  $^{90}\text{Y}$  SIR-spheres<sup>®</sup>

Source of uncertainty	Relative standard uncertainty components (%)							
	ANSTO Secondary Standard		ARI TPA		ARI Vinten		Activity	
	Type A	Type B	Type A	Type B	Type A	Type B	Type A	Type B
Electrometer accuracy		0.14	—	0.57	—	0.87	—	0.14
ESDM <sup>a</sup> of sample current	0.027	—	0.063	—	0.021	—	0.33	—
Background	0.0004	—	0.14	—	0.0071	—	0.001	—
Chamber drift correction	0.044	—	—	—	0.73	—	0.055	—
Chamber drift (no correction)	—	—	—	1.1	—	—	—	—
Non-linearity of chamber	—	0.87	—	1.1	—	1.1	—	0.87
$^{90}\text{Y}$ decay correction	—	0.022	—	0.019	—	0.037	—	0.055
Calibration factor	—	—	—	—	—	—	—	0.74
Activity loss during digest	—	—	—	—	—	—	—	0.006
Combined uncertainty	0.88		1.7		1.6		1.2	

<sup>a</sup>Experimental standard deviation of the mean.

Table 3  
Activity loss during chemical digestion

Sample	Activity loss (kBq)	Activity loss/total activity
$^{90}\text{Y}$ -m-1	$32.2 \pm 2\%$	0.002%
$^{90}\text{Y}$ -m-2	$18.5 \pm 2\%$	0.001%
$^{90}\text{Y}$ -m-3	$102.1 \pm 2\%$	0.005%
$^{90}\text{Y}$ -m-4	$133.2 \pm 2\%$	0.006%

Table 4  
Ionisation chamber calibration factors for 1 ml SIR-spheres<sup>®</sup> in a Wheaton vial

Geometry	Ionisation chamber calibration factors (pA/MBq)		
	ANSTO Secondary Standard	ARI TPA	ARI Vinten
1 ml SIR-spheres <sup>®</sup> in Wheaton vial with 34% (by volume) of $^{90}\text{Y}$ microspheres	$0.241 \pm 1.0\%$	$0.196 \pm 1.5\%$	$0.069 \pm 1.5\%$
1 ml SIR-spheres <sup>®</sup> in Wheaton vial with 44% (by volume) of $^{90}\text{Y}$ microspheres	$0.242 \pm 1.0\%$	$0.197 \pm 1.5\%$	$0.070 \pm 1.6\%$

Table 5  
Ionisation chamber calibration factors for 5 ml SIR-spheres<sup>®</sup> in a Wheaton vial

Geometry	Ionisation chamber calibration factors (pA/MBq)			
	ANSTO Secondary Standard	ARI TPA	ARI Vinten	ARI Production
5 ml SIR-spheres <sup>®</sup> in Wheaton vial with 43% (by volume) of $^{90}\text{Y}$ microspheres	$0.223 \pm 2.2\%$	$0.181 \pm 2.6\%$	$0.063 \pm 2.7\%$	$0.201 \pm 2.6\%$

the specific ionisation current value (pA/g) for the two 1 ml and two 5 ml SIR-sphere<sup>®</sup> samples dispensed from the same stock. The microspheres tended to sink when

the SIR-spheres<sup>®</sup> stock was moved away from the stirrer for dispensing. The uncertainty components and evaluation for the calibration factors for 5 ml

SIR-spheres<sup>®</sup> were similar as described before, except for the additional components of the sample mass (0.70%) and inhomogeneity of the activity concentration of the SIR-spheres<sup>®</sup> stock (1.7%).

Considering the primary solution as having a 0% microsphere concentration, it can be seen that the calibration factors increase somewhat with increasing microsphere concentration, by about 1% for 1 ml and 2% for 5 ml when the concentration increases from 0% to 44%. The density of the microspheres and that of water are almost the same. The amount of bremsstrahlung generated and absorbed by microspheres and water should be similar. The factor could be considered for the small discrepancy is how the active substances are distributed in these two types of radioactive sources. In the microspheres source, the active substances are attached to the surface of microspheres; while in the solution source, they are uniformly distributed. Further study of this effect needs to be undertaken. For the same microsphere concentration however, the calibration factors decrease greatly with increasing volume, approaching 10% depending on ionisation chamber type, showing that the volume has a more significant effect than the microsphere concentration on the calibration factor.

#### 4. Conclusion

The Secondary Standard ionisation chamber calibration factor for <sup>90</sup>Y solution may be accurately transferred to SIR-spheres<sup>®</sup> by employing a highly quantifiable chemical digestion method. The direct standard transfer is limited to a small quantity of SIR-spheres<sup>®</sup> of about 1 ml due to the difficulty of effectively digesting a large quantity of SIR-spheres<sup>®</sup> such as 5 ml. The calibration factor for 5 ml SIR-spheres<sup>®</sup> may be derived from the factor for 1 ml SIR-spheres<sup>®</sup>, although relatively large uncertainty may be introduced due to the inhomogeneity of activity concentration dispensed into 1 and 5 ml samples. Under this principle, the ARI production chamber and ARI QC TPA and Vinten chambers were calibrated for 1 and 5 ml SIR-spheres<sup>®</sup> in Wheaton vials. The capability for ARI to perform traceable activity measurements of the SIR-spheres<sup>®</sup> product was therefore developed.

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