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# Investigation of the response variability of ionization chambers for the standard transfer of SIR-Spheres<sup>®</sup>

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## Abstract

The present paper addresses the calibration of well-type ionization chambers (ICs) used at LNE-LNHB as standard transfer instruments to calibrate hospitals in the case of SIR-Spheres<sup>®</sup> <sup>90</sup>Y resin microspheres (Sirtex, Australia). Developed for interventional oncology, this radiopharmaceutical is directly injected in the liver for cancer treatment via a selective internal radiation therapy. The present work was carried out in the framework of the European project “Metrology for molecular radiotherapy” (MetroMRT). As commonly performed in radionuclide metrology for radiopharmaceuticals, the objective is to ensure the metrological traceability of SIR-Spheres<sup>®</sup> to hospitals. Preceding studies were focused on primary measurements of SIR-Spheres<sup>®</sup> based on the TDCR (Triple to Double Coincidence Ratio) method, applied after the dissolution of the <sup>90</sup>Y-labeled resin microspheres. As <sup>90</sup>Y is a high-energy  $\beta$ -emitter, the IC response strongly depends on the transport of electrons in the radioactive solution and surroundings (vial, chamber liners and materials). The variability of the IC-response due to the geometry dependence is investigated by means of measurements and Monte Carlo simulations in the case of a Vinten IC. The aim of the present study was also to propose a reliable uncertainty for ICs calibrations for the standard transfer of SIR-Spheres<sup>®</sup> to hospitals.

## Keywords

Radionuclide metrology, SIR-Spheres<sup>®</sup> standardization, <sup>90</sup>Y-labeled resin microspheres, Ionization chamber calibration, Monte Carlo simulation

## 1. Introduction

The collaborative project “Metrology for molecular radiotherapy” (MetroMRT, HLT11) initiated within the European Metrology Research Programme aimed at providing metrological support in the field of targeted radionuclide therapy (D’Arienzo et al., 2014). Molecular radiotherapy (MRT) refers to therapeutic techniques where a high-radiation dose is internally delivered to a specific target such as tumors. During the 3-year MetroMRT project (2012–2015), the participation of the Laboratoire National Henri Becquerel (LNE-LNHB) was chiefly focused on the standardization of SIR-Spheres<sup>®</sup> <sup>90</sup>Y-labeled resin microspheres (Sirtex, Australia) used in Selective Internal Radiation Therapy (SIRT) for the treatment of liver tumors (Dezarn et al., 2011). As conventionally performed in National Metrology Institutes (NMIs) for radiopharmaceuticals (Zimmerman and Judge, 2007), the aim is to provide a reliable metrological traceability between primary standards and hospitals. The interest of this study is also to respond to the need of MRT quantitative imaging applied to monitor biodistribution of <sup>90</sup>Y-labeled microspheres in tissues after therapeutic injection (Bagni et al., 2012). The purpose is to ultimately develop patient-specific dosimetry based on quantitative tomographic imaging in the case of SIRT treatments (Pasciak et al., 2014).

SIR-Spheres<sup>®</sup> product supplied by Sirtex in a specific vial contains a nominal activity of 3 GBq (at the reference date) in a 5 mL solution of sterile, pyrogen-free water for injection to patients.

Primary measurements were performed using the TDCR (Triple to Double Coincidence Ratio) method after dissolution of the <sup>90</sup>Y-labeled resin microspheres in the original Sirtex vial. The dissolution procedure developed at LNE-LNHB is detailed in Lourenço et al. (2015). A chemical digestion was

already applied (but full procedure not disclosed) by Mo et al. (2005) to establish secondary standards with ionization chambers (ICs).

The present article deals with the calibration with the Sirtex vial of the ICs used for metrological traceability at LNE-LNHB. Due to the fact that  $^{90}\text{Y}$  is a high-energy  $\beta^-$ -emitter ( $E_{\text{max}}=2279$  keV), the variability of calibration coefficients resulting from the sensitivity of the vial geometry is investigated (Coursey et al., 1993, Fenwick et al., 2014). This geometry dependence is also studied by means of Monte Carlo (MC) simulations of the Vinten IC using Geant4, a general-purpose toolkit for the simulation of the transport of particles in matter (Agostinelli et al., 2003). The problem of systematic deviations between experimental and calculated calibration coefficients observed in the case of high-energy  $\beta^-$ -emitters is also discussed. The objective is to assess a reliable uncertainty of ICs calibrations for the transfer of SIR-Spheres<sup>®</sup> standard to hospitals.

## 2. Calibration of ionization chambers for SIR-Spheres<sup>®</sup>

### 2.1. Technical description

For the transfer of the SIR-Spheres<sup>®</sup> standard, measurements were performed with two different well-type ICs commonly used at LNE-LNHB as secondary instruments: the Vinten type 671 IC of equivalent design to the IG42 IC constructed by Centronic (Woods et al., 1983, Amiot, 2004) and the Normandy IC constructed by Rib Technologie (Amiot, 2014), especially dedicated to the transfer of standards to hospitals.

The Vinten IC has a cylindrical aluminium chamber with a 10.5 L effective volume (filled with  $\text{N}_2$  at 1 MPa) including a coaxial re-entrant well (73-mm diameter, 374-mm height) made of aluminum (2-mm thick) with a polyvinyl liner placed on top (0.5-mm thick). The IC is equipped with a central aluminum-alloy electrode (2-mm thick) and it is housed in a Bakelite support (1-mm thick); surrounded by an additional homemade lead shielding (hollow cylindrical shape with 50-mm thick) to reduce the background.

The Normandy IC has also an aluminum chamber with an effective volume of about 8 L (75-mm re-entrant well diameter, 1.5-mm thick) filled with Ar gas (0.2-MPa pressure) equipped with an aluminum alloy electrode. This chamber is surrounded by a homemade shielding composed of a 5-mm-thick layer of lead and outer 2.5-mm-thick layer of steel.

Custom made of source holders are used for both ICs: one is made of Teflon<sup>®</sup> for the Normandy IC and the other of polymethyl methacrylate (PMMA) for the Vinten IC.

At LNE-LNHB, the calibration of the Vinten IC is generally carried out with specific LNHB ampoules (wall thickness of 0.61 (1) mm) filled with 5 mL of radioactive solution ( $\text{HCl}$  0.1 mol  $\text{L}^{-1}$  usually). It has to be noted that this IC is a copy of the Vinten 671 employed at the National Physical Laboratory (NPL, UK). However, the results from both NMIs are not quite comparable due to the source-to-detector arrangement, i.e. source holders and chamber surroundings.

### 2.2. Calibration coefficients

SIR-Spheres<sup>®</sup> are produced by Sirtex in a specific vial (15-mL glass vial) filled with 5 mL of a solution containing a mixture of sterile water and  $^{90}\text{Y}$ -labeled resin microspheres. The activity in the original Sirtex vial was assessed from primary measurements based on the TDCR method, applied after the dissolution of the  $^{90}\text{Y}$ -labeled resin microspheres. The ICs calibrations were carried out without vial shaking (after the sedimentation of microspheres, obtained after ~2 min). The resulting calibration coefficients were reported in Lourenço et al., (2015) with combined uncertainties of about 1.5% ( $k=1$ ), mainly due to primary measurements.

### 2.3. Variability of the IC response with vial geometry

The vial-dimensions were measured at LNE-LNHB by using a vernier caliper and from a batch of vials provided by Sirtex (about fifty). The following averaged values were obtained: wall thickness of about 2.0 (2) mm and bottom thickness of 2.8 (4) mm. Ten vials with different masses (comprised between 18.6 g and 20.6 g) were then measured filled with 5 mL of  $^{90}\text{Y}$  aqueous solution (25  $\mu\text{g g}^{-1}$  of

Y in 0.04 M HCl; activity concentration of about 200 MBq g<sup>-1</sup> per vial for the Normandy IC and 30 to 70 MBq g<sup>-1</sup> per vial for the Vinten IC). Some of these vials were previously measured with active SIR-Spheres<sup>®</sup>. The plot in Fig. 1 displays the massic current (pA per gram of solution) obtained with the ten vials in the Vinten IC. Only statistical uncertainties are considered in the plot (~0.2%). A decrease of the massic current as a function of empty-vial mass is clearly observed. This correlation yields a difference of about 14% between the minimum and maximum values. It can be observed in Fig. 1 that the variability of the massic currents (relative standard deviation~5%) is much higher than the associated uncertainties (lower than 0.3%). The same measurements were also performed with the Normandy IC and an analogous correlation is observed (Fig. 2) but with a lower maximum difference (~5%). The variability of the results is also lower (relative standard deviation ~1.5%).

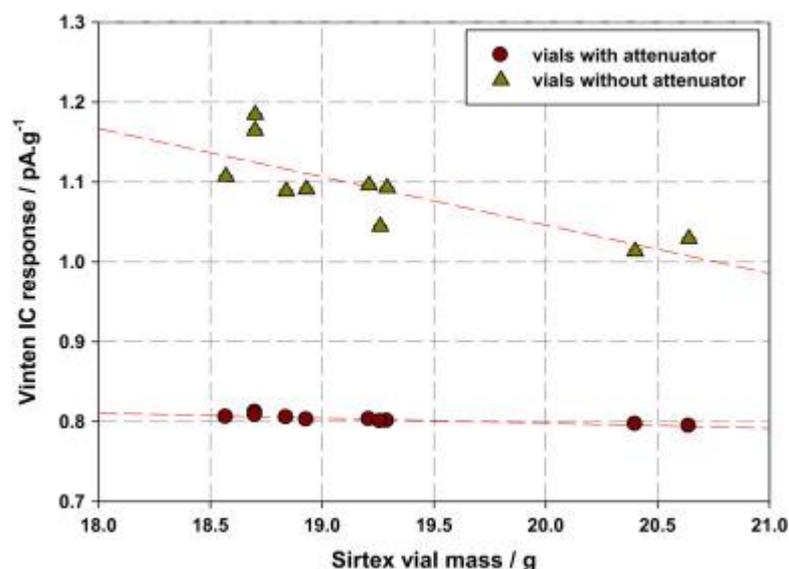


Fig. 1. Massic current as a function of mass of 10 Sirtex vials (filled with 5-mL of <sup>90</sup>Y aqueous solution) in the Vinten IC (with and without copper attenuator). Only statistical uncertainties are considered (~0.2%), here within the symbols.

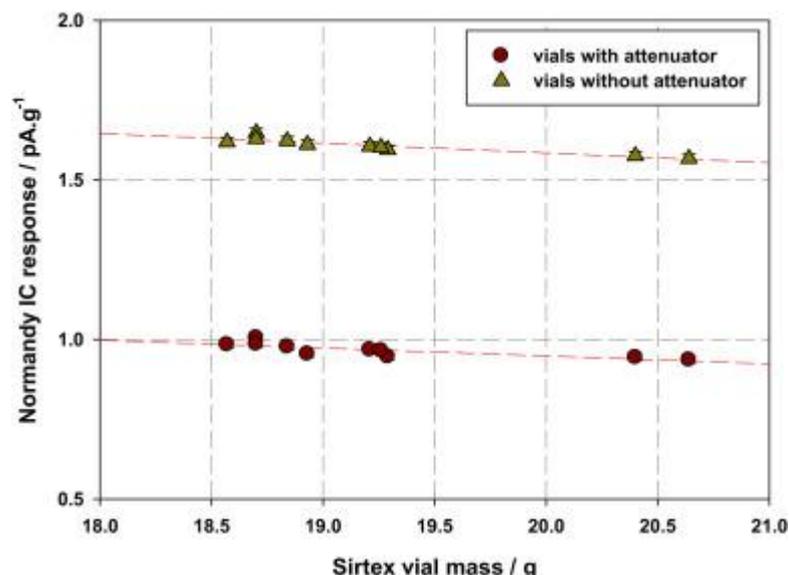


Fig. 2. Massic current as a function of mass of 10 Sirtex vials (filled with 5-mL of <sup>90</sup>Y aqueous solution) in the Normandy IC (with and without copper attenuator). Only statistical uncertainties are considered (~0.3%), here within the symbols.

The same measurements were carried out with a homemade copper attenuator (0.5-mm thick tube); a significant reduction in observed response, of about 40%, was observed for the Normandy IC (see Fig. 2) and about 26% for the Vinten IC (see Fig. 1). The massic currents depending on the measurement

configurations are reported in Table 1. In the case of the Vinten IC, the correlation is strongly reduced with a significant decrease of the variability (relative standard deviation ~0.6%). On the contrary, the correlation and the variability remain almost identical in the case of the Normandy IC.

Sirtex empty-vial mass (g)	Normandy IC response (pA g <sup>-1</sup> )		Vinten IC response (pA g <sup>-1</sup> )	
	Without attenuator	With attenuator	Without attenuator	With attenuator
18.57	1.618 (5)	0.984 (3)	1.107 (2)	0.806 (2)
18.69	1.647 (5)	1.006 (3)	1.184 (2)	0.812 (2)
18.70	1.629 (5)	0.986 (3)	1.165 (2)	0.808 (2)
18.84	1.622 (5)	0.977 (3)	1.088 (2)	0.805 (2)
18.93	1.610 (5)	0.955 (3)	1.091 (2)	0.802 (2)
19.20	1.605 (5)	0.968 (3)	1.096 (2)	0.803 (2)
19.26	1.602 (5)	0.965 (3)	1.044 (2)	0.800 (2)
19.30	1.594 (5)	0.946 (3)	1.093 (2)	0.801 (2)
20.40	1.575 (5)	0.944 (3)	1.013 (2)	0.797 (2)
20.64	1.567 (5)	0.936 (3)	1.029 (2)	0.794 (2)
standard deviation (%)	1.5	2.3	5	0.6
maximum difference (%)	5.0	7.0	14.0	2.0

Table 1. Massic current (pA per gram of solution) as a function of vial mass of ten Sirtex vials (filled with 5-mL of <sup>90</sup>Y aqueous solution) in both ICs.

For all the measurement configurations (with and without attenuator), the higher massic current was obtained with the vial at 18.69 g. Despite this vial being very close to the one weighing 18.7 g, a significant relative difference (1–2%) is observed between both vials. The same behavior was also observed in both ICs when some of the Sirtex vials of the batch (18.69 g, 18.7 g and 18.93 g) were previously measured with active SIR-Spheres<sup>®</sup>. This shift could be due to significant distortions of shape observed on the vial at 18.69 g (in fact the bottom thickness of this vial was 1 mm lower than the average value).

The measurements carried out with the batch of ten vials with increasing masses can help to assess a reliable uncertainty for IC calibration with SIR-Spheres<sup>®</sup>. It was observed that the IC response depends on the detector design and the mass of the vial as well as its geometry. Because the Normandy IC calibration for SIR-Spheres<sup>®</sup> is more robust with regards to the obtained results, it is now used at LNE-LNHB for secondary measurements of SIR-Spheres<sup>®</sup> with a conservative uncertainty equal to 5% (corresponding to the maximum difference obtained between ten vials measured) in order to consider the variability due to the Sirtex vial. In the case of the Vinten IC, the relative uncertainty should be higher than 10%. It can be also drawn from the study that this value can be significantly reduced by the use of a copper attenuator (0.5-mm thick). It could also be reduced with harmonization of vials produced by Sirtex with a more consistent mass profile; this will be recommended in the final report of MetroMRT project.

### 3. Monte Carlo calculations of calibration coefficients

Based on the measurement of the total charge generated in the gaseous region (due to electron/ion pairs created) the IC response and therefore the calibration coefficient is sensitive to the chamber design (chamber liners, type of filling gas and shielding), the nature of the solution (volume and composition), the vial dimensions, the source holder and also the radionuclide decay scheme. MC simulations of radiation-matter interactions are very useful to study the resulting effects of those properties or the addition of other elements such as liners (Ceccatelli et al., 2007, Kryeziu et al., 2007, de Vismes and Amiot, 2003). In this framework, several investigations based on the use of MC calculations to estimate calibration coefficients have already been implemented at LNE-LNHB. The Vinten IC response for many radionuclides decaying through photon cascades such as  $^{60}\text{Co}$ ,  $^{22}\text{Na}$ ,  $^{18}\text{F}$  or  $^{99\text{m}}\text{Tc}$  in LNHB ampoules were calculated using the Penelope code (Salvat et al., 2009). These investigations have shown the ability of MC calculations to estimate adequately ICs responses in the case of photon-emitting radionuclides for which an excellent agreement with experiment (lower than 1%) were obtained (de Vismes and Amiot, 2003; Amiot, 2004). This work was extended for the present study in the case of pure  $\beta^-$ -emitters such as  $^{90}\text{Y}$ .

#### 3.1. Methods

In this study, the Geant4.10.0 version was used to simulate the mean energy deposited in the effective volume of the Vinten IC. The geometry modeling (including source-detector arrangement and surroundings) was implemented using detailed drawings provided by the manufacturer and x-ray of the chamber, and a filling gas pressure determined in de Vismes and Amiot (2003).

The original Sirtex vial was modeled as a pure glass material ( $\text{SiO}_2$ , density of  $1.32 \text{ g cm}^{-3}$ ) filled with 5 mL of a mixture of the resin microspheres (30% of the total solution) and pure water (70% of the total solution). The microspheres settled at the bottom of vial were simulated as a homogeneous volume. The chemical composition was defined from the hydrated form given by Dias and Shapka (2001) and taking into account water in the interstitial spaces between spheres (40% water and 60% resin microspheres): carbon (31.9%), hydrogen (7.7%), oxygen (50%) and sulfur (10.3%). The mass per unit volume of  $1.06 \text{ g cm}^{-3}$  was measured at LNE-LNHB.

The emission of  $\beta^-$ -particles is randomly generated as a uniform distribution in the whole radioactive volume (corresponding to microspheres volume settled at the bottom of vial) and uniformly in all possible random directions with initial electron energies drawn from a calculated  $\beta^-$ -spectrum. These source specifications are implemented using General Particle Source (GPS) module available in Geant4.

The calibration coefficient in terms of  $\text{pA MBq}^{-1}$  is calculated using the total mean energy  $E$  (eV) deposited in the gaseous region according to the expression

$$C = e \frac{E}{W} 10^{18}$$
, assuming that the charge collection in the gas is 100%;  $e$  (coulomb) is the electron charge and  $W$  (eV) the mean energy required to produce one ion pair in the filling gas (equal to 34.8 (2) eV for nitrogen as given in ICRU Report 31 (1993)).

#### 3.2. Calculation of calibration coefficients in the case of pure $\beta^-$ -emitters

Depending on  $\beta^-$ -emitter maximum energies, the total energy deposited in the IC gas region can mainly be due to the production of bremsstrahlung photons along the track of electrons in matter. To test the physics models, simulations were performed with three sets of electromagnetic (EM) models available in Geant4 and which are able to perform adequately the EM processes (Chauvie et al., 2004). The theoretical model “G4EmStandard” and both the low-energy models: “G4EmLivermore” and “G4EmPenelope” which corresponds to a re-engineering in Geant4 of physics models from the Penelope code (Salvat et al., 2009). Many papers in the recent literature have shown that the proposed models are able to predict in a fairly good way the simulation of the transport of photons and electrons in matter, even if the Penelope model seem slightly preferable over the other two in the range of energy from few eV to few MeV (Pandola et al., 2015, Ivanchenko et al., 2011).

The response of the Vinten IC was simulated here using the specific LNHB ampoules (filled with 5 mL of aqueous solution) for three pure  $\beta^-$ -emitters:  $^{90}\text{Y}$  ( $E_{\text{max}}=2279$  keV, 1st forbidden unique transition),  $^{89}\text{Sr}$  ( $E_{\text{max}}=1495$  keV, 1st forbidden unique transition) and  $^{32}\text{P}$  ( $E_{\text{max}}=1710$  keV, allowed transition). The respective spectra were computed with the homemade BetaShape program (Mougeot, 2016) using the decay-scheme parameters from the Table of radionuclides (Bé et al., 2006).

The calibration coefficients obtained for  $^{90}\text{Y}$  decay are:  $3.50$  (5)  $10^{-1}$  pA MBq $^{-1}$ ,  $3.31$  (5)  $10^{-1}$  pA MBq $^{-1}$  and  $3.25$  (5)  $10^{-1}$  pA MBq $^{-1}$ , respectively for “G4EmPenelope”, “G4EmLivermore” and “G4EmSandard” EM physics models. Regarding these results, large underestimations of the calculated values (of about 30%) are observed when compare to the experimental value ( $5.06$  (7)  $10^{-1}$  pA MBq $^{-1}$  for  $^{90}\text{Y}$ ). The typical uncertainty components related to MC calculations is given in Table 2. It should be noted that the implementation of other EM physics models does not reduce the large discrepancies between experimental and simulated values; the maximum difference between three models remains lower than 8%. The same behavior was also obtained with  $^{32}\text{P}$  and  $^{89}\text{Sr}$  decays with discrepancies of about 40% and 41% respectively. This underestimation was already observed with MC Penelope calculations performed at LNE-LNHB for the Vinten IC and another which is the Vacutec IC filled with an Ar–Xe gas mixture (Amiot, 2014).

Uncertainty components	%
$^{90}\text{Y}$ decay scheme	0.4
Shape factor of beta spectrum	0.35
computed mean-energy deposited	0.8
physics models	0.5
W-value required for e $^-$ /ion pair creation	0.57
<b>combined relative uncertainty</b>	<b>1.5</b>

Table 2. Typical uncertainty components of the MC calculation of the Vinten IC response in the case of  $^{90}\text{Y}$ .

The sensitivity to the calculated  $^{90}\text{Y}$   $\beta$ -spectrum was tested by using three different experimental shape factors depending on the term  $W$  representing the  $\beta$  particle energy:  $1,1 - 0.0064 \times W$  and  $1,1 - 0.0114 \times W$  (Mougeot, 2016); the result shows only a 1% variation of the IC response.

It should be mentioned that for the three  $\beta^-$  decays tested, the effective contribution of the bremsstrahlung process to the total mean energy deposited in the gas region was estimated to about 5% for  $^{90}\text{Y}$ , 90% for  $^{32}\text{P}$  and close to 100% for  $^{89}\text{Sr}$ . In the case of the  $^{90}\text{Y}$ , the major part of the total energy deposited in the gas region is due to the initial electrons from the  $\beta$ -spectrum. Additional simulations were performed by varying the interpolated cross section of the bremsstrahlung at the boundaries of the associated uncertainties ( $\pm 10\%$ ). These fluctuations have finally led to a small variation of the total energy deposited (2% maximum difference).

Regarding these investigations, it seems that the IC response of the Vinten IC cannot be reproduced by means of MC calculations in the case of pure  $\beta^-$ -emitters while it works for photons emitters (Amiot et al., 2012, Bochud et al., 2015). Despite the use of different ICs, the kind of spectrum and energy range or EM physics models used for pure  $\beta^-$ -emitters, the large discrepancies between experimental and calculated calibration coefficients was not reduced. Up to now this problem remains unsolved and requires advanced investigations. For that reason, MC simulations were performed in the following only to assess the relative variability of IC response due to the vial geometry dependence for secondary measurements of SIR-Spheres $^{\text{®}}$ .

### 3.3. Vinten IC response variability due to Sirtex vial by means of MC calculations

The variability of the Vinten IC response for Sirtex vials was also investigated by means of MC simulations. Calculations were first performed for two representative Sirtex vials among the ten measured (dimensions implemented in manner to be close to both representative vials weighing 20.4 g

and 18.93 g) filled with 5 mL of  $^{90}\text{Y}$  aqueous solution. A relative difference of 6% between both vials was obtained on calculated calibration coefficients. This result is consistent with the difference of 8% obtained with measurements. The impact of the copper attenuator (0.5-mm thick) was also simulated. As observed experimentally, the MC calculations yield a decrease of the IC response (~20%). Furthermore, as expected, the relative difference between both modeled vials is strongly reduced with the usage of copper attenuator (0.5% with simulated model compared with 0.6% for experiment).

The IC responses were also calculated for the two representative Sirtex vials (20.4 g and 18.93 g) filled with resin microspheres (as described in Section 3.1) in order to check for potential differences with the behavior observed with  $^{90}\text{Y}$  aqueous solution. The simulations performed by varying the wall thickness from 1.8 mm to 2.0 mm lead to a difference on the Vinten IC response of about 3.5%. The same MC calculations carried out by varying the bottom thickness from 2.2 mm to 3.2 mm yield a difference of about 1%. The influence of the density of glass was also tested. It appears that the variation of the density (1.32–1.33 g cm<sup>-3</sup>) entails an increase of the IC response of about 4%. Contrary to the case of aqueous solution, the MC calculations related to resin microspheres slightly underestimate the effect of the variation of the vial geometry compared with experiments. These deviations could be due to the composition of the resin microspheres used for the simulation or their geometrical modeling.

#### 4. Discussion and conclusions

In the framework of SIR-Spheres<sup>®</sup> standardization at LNE-LNHB, the problem of the uncertainty of ICs calibration coefficients due to the variability of the original Sirtex vial was investigated by means of experimental measurements and MC calculations.

Experimental results were obtained with vials of different masses (filled with 5 mL of  $^{90}\text{Y}$  aqueous solution) provided by Sirtex. A correlation between the IC response and empty-vial mass was observed with both calibrated ICs: Vinten 671 IC (filled with N<sub>2</sub> gas) and Normandy IC (filled with Ar gas). The differences of the ICs responses between Sirtex vials were higher with the Vinten IC (14% maximum difference) than with the Normandy IC (5% maximum difference). Additional measurements carried out with a 0.5-mm-thick copper attenuator showed that these differences are significantly reduced in the case of the Vinten IC (~2%).

The variability of the Vinten IC response with the vial geometry (both wall thickness and bottom thickness) was also studied by means of MC calculations. The problem of the systematic underestimation of the IC response was addressed but it has not been possible to give a definitive explanation on its origin. More investigations are on-going in order to understand that and to improve MC calculations. Regarding relative variations, the simulation results were more consistent with experiments for the study of the IC response variability with the variation of Sirtex vial geometry filled with aqueous solution. The extension of MC calculations to the modeling of microspheres led to a slight underestimation of the influence of the Sirtex vials on the Vinten IC response. This problem could be due to the composition of the resin microspheres used for the modeling or due to the fact that the  $\beta^-$ -emission is considered as uniform in the whole volume of microspheres.

Finally, it can be drawn from the present study that the Normandy IC calibration for SIR-Spheres<sup>®</sup> is more robust with regards to the variability of the Sirtex vials. In consequence, this transfer instrument is now used at LNE-LNHB for secondary measurements of the  $^{90}\text{Y}$ -labeled resin microspheres with a relative conservative uncertainty of 5% ( $k=1$ ). In the case of the Vinten IC, the uncertainty, higher than 10%, can be significantly reduced by the use of a copper attenuator. A harmonization of vials produced by Sirtex with a more consistent mass profile could also improve the robustness of ICs calibrations for SIR-Spheres<sup>®</sup>.

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