POLITECNICO DI TORINO

Corso di Laurea magistrale in Ingegneria energetica e nucleare

TESI DI LAUREA

Uncertainty in activity measurements using radionuclide calibrators due to source geometry effects

Relatori:
Prof. G. Coppa (DET)
Dott.sa Clarita Saldarriaga Vargas (SCK·CEN, Belgio)
Dott. Jérémie Dabin (SCK·CEN, Belgio)

Candidata:
Alba Carbutti

A.A. 2017/2018

For those who never give up.

Ringraziamenti

Desidero ringraziare i miei mentors Clarita e Jérémie per tutti i loro insegnamenti, per la passione che hanno fatto crescere in me, per l'aiuto, la pazienza e il tempo che mi hanno dedicato. Ringrazio SCK CEN per la possibilità che mi ha dato di lavorare a contatto con una realtà nuova, giovane e stimolante e il dottor Kristof Baete e tutto l'ospedale di Leuven per avermi fornito ulteriori mezzi per il completamento di questo progetto e soprattutto per avermi fatto lavorare al loro fianco.

Dal profondo del cuore ringrazio il professore Gianni Coppa che mi ha seguito in questo lavoro, per l'immenso aiuto e supporto. A lui devo questa tesi e la fine di questo percorso ma soprattutto la mia più immensa gratitudine per aver creduto in me.

Il ringraziamento più grande mi è doveroso farlo a chi mi ha sempre supportata: la mia famiglia, i miei genitori, le mie zie e zii e i miei nonni. Senza il loro appoggio non sarei mai andata così lontano.

I ringraziamenti più vivi invece vanno a chi mi ha sempre spinta oltre quei limiti che solo io vedevo, oltre le mie paure: le mie migliori amiche, Eliana e Giulia, la mia seconda famiglia in via Fratelli Carle in tutte le sue componenti, i ragazzi di Boeretang, e tutti gli amici che mi sono stati accanto in questi anni, i vecchi, i nuovi e quelli che ho ritrovato.

In ultimo vorrei ringraziare un luogo, Boeretang, per tutto quello che ha significato, per avermi fatto ritrovare la forza e avermi fatto vedere un'altra me. Lì ho trovato la pace e chi, con il suo immenso appoggio, mi ha supportata, sopportata e spinta verso questo traguardo in tutti questi ultimi mesi. A questo luogo, a questa persona, e anche a me stessa dedico la mia immensa soddisfazione di oggi.

Abstract

In nuclear medicine is fundamental the use of devices called radionuclide calibrators for the activity measurements of radiopharmaceutical. These radiopharmaceuticals have to be administered to the patients for therapeutic or diagnostic use. A radionuclide calibrator basically consists in an ionization chamber, with an operating principle based on the reading of a current generated by charged particles. These particles ionize the gas, where a pair of ions is produced with the resulting difference of potential, which moves to the electrodes of opposite sign. The electrodes discharge, producing an electrical pulse read by the device and displayed, thanks to calibration factors, in terms of activity. The activity readings performed with these devices are affected by the particle energy and by the amount of emitted radiation, moreover they suffer the geometry effect due, for example, to the type of container, its position inside the chamber, the volume of solution which fills it.

The aim of this work was to study the uncertainties due to source geometry effects on activity measurements using radionuclide calibrators.

Activity measurements were performed in Fidelis Secondary Standard Radionuclide Calibrator, available at the Belgian Nuclear Research Centre (SCK•CEN), and in other clinical radionuclide calibrators available at the University Hospital of Leuven. Those calibrators belong to two of the most commonly used brands of medical devices: Veenstra (now owned by Comecer) and Capintec. Reference measurements were made using the Fidelis and a source geometry consisting of a Schott 10 ml glass vial and were used for the comparison with all the results obtained during all the tests performed. For the mentioned reference system, calibration factors for all the radioisotopes chosen were available. The activity measurements obtained in this reference system represented the true activity. From the activity in the Schott vial 10 ml and the weight of active solution inside it, the true activity concentration (expressed in MBq/ml) was determined. The true activity in any other sample prepared from the reference radioactive solution was then determined gravimetrically.

The following radionuclides were used for the tests on geometry effect: ^{99m}Tc, ^{111}In, ^{123}I, (gamma emitters); ^{18}F, ^{68}Ga (positron emitters); ^{131}I, ^{90}Y (beta emitters) and ^{223}Ra (alpha emitter). From these group of radionuclides only ^{90}Y had a decay which did not result in the emission of any gamma photon, thus measurements of ^{90}Y in radionuclide calibrators relied mainly on bremsstrahlung radiation. Each sample was tested in different clinical containers, chosen between syringes and vials. During the test, the measurements for each of these containers were performed for different volumes, filling the sample by a gravimetric process. The first volume was directly made by the solution extracted from the Schott vial while the additional volumes were filled by water, in order to maintain the same activity value during all the process. Each measurement was carried out in Fidelis, in a Comecer and in a Capintec radio calibrators.

For a more detailed study about the uncertainties, other parameters which influence the performance of the radionuclide calibrators were also studied, including: the position of the sample inside the ionization chamber, the temperature and the humidity in the environment and

the differences due to the geometric tolerance of the reference vial. All the tests on these parameters were investigated using only the Fidelis radiocalibrator. The tests for evaluating the effect of the temperature and the position of the sample were performed using a long-lived check source of ^{137}Cs, while the tests on the geometric tolerance were performed using ^{99m}Tc.

Finally, performing quality control (QC) tests on Fidelis was required in order to evaluate the correct functionality of the device. In this work it is used a solid source of ^{137}Cs with an activity of about 9.6 MBq.

In general, the QC tests and the characterization tests have shown a correct operational functionality of Fidelis RC. For this reason, all the uncertainty obtained from the characterization tests were used in the computation of the overall uncertainty on the true activity used in geometry tests.

From the geometry tests performed, it was possible to see that the volume effect is lower if compared with the effect of the different containers.

The difference noticed for the different containers were, in fact, not negligible as the ones obtained in the accuracy tests.

During all the experiments, in fact, some radioisotopes, like for example ^{99m}Tc, ^{123}I and ^{111}I have shown great differences between samples, depending on the different energy photons emitted and on the materials and the shape of the containers (like for example plastic syringes and glass vials).

The accuracy on the supplier vial presented unexpected results for three radiopharmaceuticals: ^{123}I, ^{223}Ra and ^{90}Y. The difference between the activity measured from the supplier and during the test higher than the 5%.

Sommario

Nel campo della medicina nucleare è fondamentele l'uso di dispositivi chiamati calibratori di attività o calibratori di dose per la misura dell'attività dei radiofarmaci. Nello specifico, questi radiofarmaci sono somministrati ai pazienti per scopi terapeutici o diagnostici. I calibratori di attività consistono principalmente in una camera a ionizzazione che sfruttala presenza di particelle cariche che, attraversando un gas immerso in un campo elettrico, ne provocano la ionizzazione. Poichè le particelle che si formano sono immerse in un campo elettrico, gli ioni e gli elettroni migrano verso gli elettrodi di segno opposto. La scarica di questi elettrodi genera quindi un segnale elettrico letto dal dispositivo e tradotto, attraverso opportuni fattori di calibratura, in termini di attività. La lettura di questo valore sarà influenzata dall'energia delle particelle, dalla quantità di radiazione emessa e anche dalla geometria del campione, quale ad esempio il tipo di contenitore in cui è contenuto, la posizione all'interno della camera di ionizzazione o il volume di sostanza presente al suo interno.

Lo scopo di questo lavoro è stato lo studio delle incertezze, dovute agli effetti di differenti condizioni geometriche dei campioni, sulla misura dell'attività di diversi radionuclidi sfruttando tre diversi marchi di calibratori di dose.

Le misure di attività sono state effettuate utilizzando Fidelis Secondary Standard Radionuclide Calibrator, disponibile nel centro di ricerca nucleare belga SCK•CEN e in altri calibratori di dose disponibili nell'ospedale universitario della città di Leuven. Questi ultimi dispositvi appartengono a due dei marchi più comunemente utilizzati nell'ambito clinico-ospedaliero: Veenstra (ora noto come Comecer) e Capintec.

Tutte le misurazioni di riferimento, per ogni esperimento, sono state effettuate utilizzando il calibratore di dose Fidelis abbinato alla fiala in vetro (marchio Schott) da 10 ml. Questi valori di riferimento sono state usati come metro comparativo rispetto alle misurazioni di attività effettuate in tutte le differenti configurazioni, geometrie e nei vari calibratori e pertanto verrano descritte in tutto l'elaborato come attività di riferimento o attività reale.

In questo sistema di riferimento, scelto come base comparativa per questo lavoro, i fattori di calibratura per tutti i radioisotopi esaminati erano disponibili.

Partendo dall'attività di riferimento misurata all'interno della fiala Schott e dal peso della soluzione radioattiva in esame, è stato possibile calcolare la concentrazione di attività di riferimento (espressa in MBq/ml), imponendo che tutte le sostanze rispondessero alla ipotesi di densità unitaria.

Partendo dal valore di concentrazione di attività ottenuto è stato quindi possible determinare l'attività "reale" per ogni altro campione sfruttando un metodo gravimetrico, quindi basato sul peso della sostanza presente all'interno di ogni differente contenitore.

I test per valutare gli effetti delle geometrie sono stati effettuati sui seguenti radionuclidi: ^{99m}Tc, ^{111}In, ^{123}I, (emettitore gamma); ^{18}F, ^{68}Ga (emettitore di positroni); ^{131}I, ^{90}Y (emettitore beta) and ^{223}Ra (emettitore alpha).

Tra tutti questi radionuclidi solo ^{90}Y presentava un decadimento esclusivamente di tipo beta senza alcuna emissione di raggi gamma motivo per cui i cui valori di attività letti dai calibratori di dose erano interamente riferiti a radiazioni dovute a bremsstrahlung.

Tutti i campioni sono stati testati in molteplici contenitori di uso medico, scelti tra siringhe e fiale in base alle risposte di un questionario che è stato somministrato ai principali ospedali del Belgio. Durante il test le misurazioni in ogni contenitore sono state effettuate variando i volumi di soluzione al loro interno, riempendo i campioni attraverso un processo gravimetrico. Il primo volume, in generale, è stato sempre generato direttamente a partire da una soluzione radioattiva contenuta in una fiala Schott (dalla quale è stata calcolata l'attività di riferimento) determinando il valore di attività durante tutto il procedimento. Perchè questo valore restasse sempre uguale, tutti i volumi presi in considerazione successivamente al primo per le misurazioni, sono stati ottenuti aggiungendo acqua distillata. Le misurazioni sono state tutte effettuate sia nel calibratore di dose Fidelis che in quelli di marchio Comecer e Capintec.

Per uno studio più approfondito e accurato delle incertezze sono stati studiati poi ulteriori parametri di influenza sulla performance dei calibratori di dose, tra cui: la posizone del campione all'interno della camera di ionizzazione, la temperatura e l'umidità dell'ambiente di lavoro e le differenze dovute alla tolleranza geometrica della fiala di riferimento. Questi parametri sono stati controllati performando esperimenti esclusivamente nel calibratore Fidelis. I test per valutare l'effetto della temperatura dell'ambiente di lavoro e della posizione del campione all'interno del macchinario sono stati effettuati utilizzando una fonte di ^{137}Cs (attività di circa 9.6 MBq) fornita in dotazione con il macchinario stesso, metre i test sulla tolleranza geometrica sono stati effettuati utilizzando una sorgente di ^{99m}Tc.

In ultimo sono stati effettuati i test per il controllo della qualità (QC tests) del macchinario Fidelis che erano richiesti per valutare il corretto funzionamento del dispositivo. Per tutti quest'ultimi è stata utilizzata la sorgente di ^{137}Cs sopracitata.

In generale, i QC test hanno mostrato un corretto funzionamento del macchinario quindi si è ritenuto possibile utilizzare tutte le incertezze ottenute attraverso lo studio dei vari parametri di influenza del dispositivo per il conteggio dell'incertezza generale dell'attività reale calcolata con i parametri di riferimento sopra citati.

Dai test sulle geometrie effettuati è stato possibile notare che l'effetto che hanno i differenti volumi all'interno dei campioni è minore se comparato all'effetto che ha l'utilizzo di campioni di forme e materiali differnti (siringhe o fiale). Durante tutti gli esperimenti, infatti, alcuni radioisotopi (come ad esempio ^{99m}Tc, ^{123}I and ^{111}I) hanno mostrato differenze molto marcate tra i vari campioni, dipendenti dalla diversa energia dei fotoni, dai materiali e dalla forma dei contenitori.

Notevoli differenze sono state anche riscontrate nella misura dell'accuratezza dei valori di attività dichiarati dai fornitori dei radiofarmaci, in particolar modo per tre distinti radionuclidi ^{123}I, ^{223}Ra e ^{90}Y: in tutti e tre i casi la differenza tra l'attività misurata durante il test in laboratorio e quella fornita superava il 5%.

Results and discussion

INTRODUCTION

1 Ionizing radiation

An *ionizing radiation* is a radiation which carry an amount of energy sufficient for displacing electrons from atoms or molecules, producing in this way *ions*. Typical sources of these radiation are unstable substances, called radioisotopes or radionuclides, capable of changing their chemical properties and release of energy in the form of charged (e.g. α particle, β particle) or uncharged particles and electromagnetic rays (e.g. neutrons, γ rays, X-rays). In the first case, the radiation is called "directly ionizing" in the second case "indirectly ionizing".

In the case of *charged particles*, that generate directly ionizing radiation, thanks to the Coulomb interactions occurring between these particles and the absorber's orbital electrons, the energy is deposited directly in the medium (D. L. Baily, 2014).

In the case of neutral particles (without charge), their passage through the medium generate a deposition of their energy in it, creating an indirect ionization. This process consists into two steps where first the particle "releases or produces a charged particle in the absorber" (D.L. Bailey, 2014) and only in the second step it "deposits at least part of its kinetic energy in the absorber" (D. L. Baily, 2014), exactly in the manner discussed for the directly ionizing charged particles.

The type of radiation, their energy, the geometrical and physical characteristics of the absorbent material (density, thickness…) determine the *power of penetration* of ionizing radiation (Fig. 1).

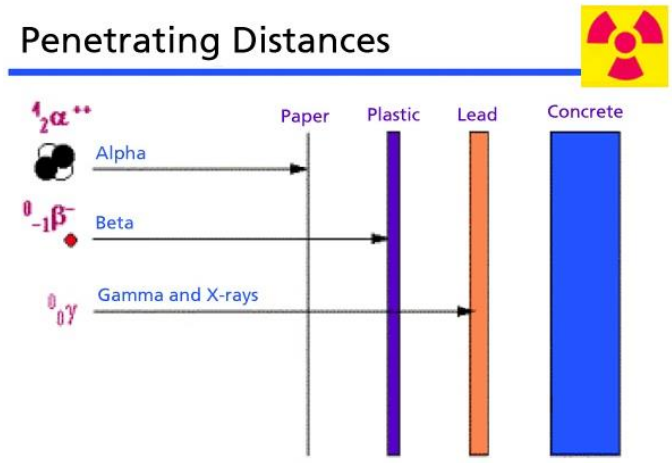


Fig. 1: Penetrating distances for α, β, γ and x-ray radiation (GTCCEIS, s.d.).

Directly ionizing radiations[1]

- Alpha particles are energetic, positively charge particles consisting in 2 protons and 2 neutrons (like helium nuclei). These particles are highly energetic and, because of their high

[1] From Principles of radiation protection (Environmental Health and Safety - Washington University, 2006), from Physics for radiation protection (Martin, 2013) and from Nuclear medicine and physics (D. L. Baily, 2014)

mass and their slow velocity (compared to other particles), their interaction with the matter occur more easily even if they are less capable to penetrate in it.
The effects on health provided by these particles depend on the kind of exposure. In general, alpha particles cannot overcome a thickness bigger than the outer layer of the skin, so they are the most dangerous in the case of inhalation, ingestion, or absorption into blood stream.

- Beta particles can be either negative (electrons) or positive (positrons). They are more penetrating than alpha but are less damaging over the same possible travelled distance. An example of beta particles emitters is given by ^{131}I, ^{90}Y (negative emitters) ^{18}F and ^{68}Ga (positive emitters).

When a collision between beta particle and a positron occurs, the achievable result, for sufficiently low energies, is their annihilation with a consequent emission of two gamma ray photons (with an energy of 511 keV), readable from the medical devices commonly available in the hospitals.

Indirectly ionizing radiations

- Gamma ray is an electromagnetic radiation emitted by the nucleus of an atom as a means of releasing excess energy. It is a photon and its emission often occurs in combination with alpha or beta particles. This kind of radiations have neither charge nor mass and are very penetrating, thus representing a hazard not only for the whole human body but also for some materials.

- Characteristics X-rays are high-energy photons produced from the excess of energy associated with the change in electron position in the atom (the movement of electrons between energy shells, from a higher to lower energy levels). X-rays have essentially the same properties as gamma rays even if they are less energetic and penetrating.

- Bremsstrahlung is an electromagnetic radiation produced by a change in acceleration of a charged particle due to a deviation caused by another charged particle . For the conservation of energy, the kinetic energy lost from the moving particle during the process (acceleration or deceleration) is reemitted in the form of radiation (typically a photon).

When X and gamma-ray photons interact with matter they could cause ionization in at least three different ways, depending on their energy (Fig.2):
1. The interaction for low-energy photons is typically due to photoelectric effect. In this case, all the photon's energy is transferred to an electron which is consequently ejected from the atom.
2. Intermediate-energy photons interactions are mostly caused by Compton effect. In this case, there is a direct interaction between the photon and electron with subsequent photon scattering in a new direction (less energy than the initial one) and electron motion caused by the incoming energy.
3. Nuclear and electronic pair production occur when photons, with an energy greater than 1.02 MeV, are replaced by an electron-positron pair which behave as directly ionizing radiation.

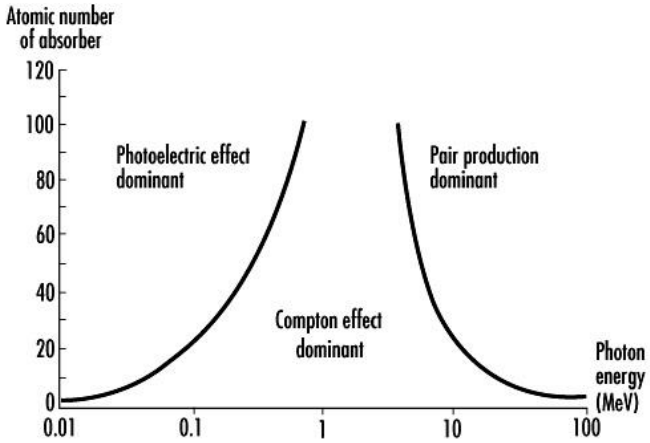


Fig. 2 Relative importance of the three principal interactions of photons in matter (http://www.ilocis.org/documents/chpt48e.htm)

2 Radioactivity

Radioactivity process involves elements with an unstable atomic nucleus and it refers to the particles or to the radiation emitted from these nuclei as a result of their instability. The most commonly emitted radiations are alpha, beta and gamma.

The radioactive decay is a probabilistic phenomenon so, even if it is not possible to know the exact moment in which one specific atom will decay, thanks to the statistical behavior of many atoms it is possible to make a prediction about the process (Martin, 2013).

The number of decays per unit time, produced from each radioactive sample is called total Activity, or *A*. This parameter's unit of measurement is the Becquerel (Bq), defined as the activity of a radioactive material's quantity in which one nucleus decays per second (Martin, 2013). It is equivalent to an inverse second (s^{-1}).

The parameter used to describe the activity behavior of a specific radionuclide are (Martin, 2013):

- Half-life ($t_{1/2}$): time of decay necessary to the radionuclide for reaching the half of the initial activity value.
- Mean lifetime (τ): average lifetime of a radioactive particle before decay (s).
- Decay constant (λ): it is the inverse of the mean lifetime $1/\tau$ (s^{-1}).

Defining *N(t)* the number of particles at time t, the total activity can be written as (Patel, 2011):

$$A = -\frac{dN}{dt} = \lambda N \tag{1}$$

This specific decay process as an exponential behavior is described by the equation 2:

$$\frac{dN}{dt} = -\lambda N \tag{2}$$

The solution of this differential equation is:

$$N(t) = N_0 * e^{-\lambda t} \quad (3)$$

Where N_0 is the number of particles at the initial time.

The main kinds of decays are (Loveland, Morrisey, & Seaborg, 2006):

- Alpha decay: an atomic nucleus emits an alpha particle (helium nucleus) transforming itself into a new atom with a mass number smaller by 4 units and an atomic number smaller by 2 units with respect to the initial one. This kind of decay is typical in the case of heavy nuclides.

A typical example of an alpha emitter used in nuclear medicine is given by ^{223}Ra (Radium).

- Beta decay: a beta ray (electron or positron), and a (anti)neutrino are emitted from an atomic nucleus. In beta minus decay, a neutron decays into a proton, an electron, and an antineutrino. In beta plus decay, a proton decays into a neutron, a positron, and a neutrino.

In nuclear medicine, common used beta emitters are ^{90}Sr that decays in ^{90}Y, beta emitter itself and ^{131}I used for therapeutic applications. Common used positron emitters are ^{18}F and ^{68}Ga.

- Gamma decay: this process is described as a spontaneous electromagnetic phenomenon where a nucleus change its energy state passing from a higher to a lower one thanks to a photon emission or more generally to an electromagnetic radiation emission (Matis, 2000). During this whole process the number of protons (and neutrons) in the nucleus remains unchanged. This kind of radiation is the most useful for medical purposes, though it is the most dangerous because of its ability to penetrate large thicknesses of material.

Some of the most common isotopes with this characteristic emission are ^{51}Cr, ^{111}In, ^{99m}Tc, ^{123}I, ^{131}I.

- Internal conversion: From Modern Nuclear Chemistry is explained as in this process, “the same excited nucleus transfers its energy radiationlessly to an orbital electron that is ejected from the atom” (Loveland, Morrisey, & Seaborg, 2006). In this way, there is an internal conversion because the electron is emitted from the atom but not from the nucleus, so the number of atom nucleus elements remains the same. The ejection of the electron produces a hole that is consequently occupied by another electron coming from a higher level of energy. This electron was available at a level of energy higher than the one necessary in the new position and, because of this exceeding energy, during this process, a characteristic X-ray or Auger electrons (or both) is emitted.

In nuclear medicine a common isotope that exhibits this kind of decay is ^{99m}Tc.

- Electron capture (Loveland, Morrisey, & Seaborg, 2006): during this phenomenon, an electron from the inner-orbitals is captured by the positively charged nucleus. A neutron is generated starting from the proton with a consequent emission of a neutrino. This process reduces the atomic number by one without changing the mass of the atom.

In nuclear medicine, the most common isotopes that exhibit this kind of process are ^{51}Cr, ^{111}In, ^{123}I.

3 Nuclear medicine

Nuclear medicine (NM) is a specific branch of medicine in which radioactive substances (called radiopharmaceuticals) are used for the treatment or the diagnosis of diseases.

Specific radionuclides are linked to chemical compounds or to specific pharmaceuticals to obtain substances that, thanks to their physical and biochemical characteristics, can reach the organ that have to be observed and/or treated. “The design of these compounds is based solely upon physiological function of the target organ” (Santos, 2007). A radiopharmaceutical mainly consists of two components: the *carrier*, which is a molecule with biological functions of transmission, and the *radioactive nuclide* (Aerts A., 2014). The first one allows the radionuclide to reach the specific organ, while the second, combined with particular diagnostic instrumentation, enables the follow up of the distribution in the body of the radiopharmaceutical. The 'diagnostic' radiopharmaceuticals then allow us to figure out exactly where is the cancer and what is its biological behavior. The properties of the radiopharmaceutical from attaching specifically in cancer cells can also be exploited for therapeutic purposes replacing the diagnostic radionuclide with another one able to emit corpuscular radiation with a lethal effect only for the cells with which they come into contact (i.e. beta- and alpha particles); in this way, the radiopharmaceutical conveys the therapeutic agent specifically at the site of disease. Such radionuclides are used for targeted radionuclide therapy (TRNT).
Alpha and beta emitters are typically used to treat of the disease (killing the cells), thanks to their capability to be absorbed as near as possible to the emission point. For diagnostic purposes, radioisotopes which emit gamma radiation predominantly (with a suitable range of energies for the gamma cameras) are used in vivo. For this reason, alpha and beta radiation are most common in the field of treatment of the disease, while gamma emitters are used most commonly in the field of the diagnosis.

Absorption of ionizing radiation energy can cause damage not only to the tissues that must be treated but, more generally, it could be a hazard for the patient. For this reason, it is necessary to avoid any possible unmotivated overexposure of the patient, maintaining the prescribed activity under (or at least at the same level of) the value of activity needed to obtain an image sufficiently clear or to provide a treatment with the maximum possible benefit. So, it is important to determine accurately the amount of activity of radiopharmaceutical before it is administered to the patient and ensure that the patients receive the correct dosage: a too low activity may result in an image with an inadequate diagnostic information or in an inefficient treatment, whereas too much activity will result in a higher and unnecessary exposure of the patient.

There are approximately one hundred radioisotopes used in NM diagnosis, therapy, and research (Matis, 2000). Some of the radioisotopes most frequently used for diagnosis are ^{99m}Tc, ^{18}F, ^{123}I and ^{111}In; while for therapy ^{131}I is the most common (Yeong, Cheng, & Ng, 2014). By 1970, 90 percent of the 8 million administrations per year of radioisotopes in the United States utilized either ^{131}I, or ^{99m}Tc ((CPEP), Contemporary Physics Education Project, 2003). One of the most common radioisotope used in diagnosis field is the ^{99m}Tc, for its specific

characteristics: half-life of 6 hours, gamma decay (main emission energy of 140 keV) and for its ready availability thanks to the high availability of ^{99}Mo-^{99m}Tc generators. ^{99m}Tc is used for brain, bones, liver, spleen, kidney, lung, and thyroid imaging as well as for blood-flow studies (World Nuclear Association, 2018).

For therapy purpose, the most used radiopharmaceutical is the radioiodine (^{131}I) which takes advantage of the affinity of that molecule for the thyroid. This radioisotope emits beta and gamma radiation and is commonly used in the thyroid treatment because this organ absorbs nearly all the iodine in the human body. So, when the radioiodine is injected into the body, in liquid or capsule form, it concentrates in thyroid cells, and the emitted radiation can destroy all the cells (including cancer cells) with a negligible effect on the rest of the body.

The medical radionuclides in which this study was focused are listed in Tab. 1 (LNHB, 2017).:

Table 1 – Main characteristics of used radionuclides

Radionuclide	Application	Decay mode and branching	T1/2	Eα (MeV)	Eβmax (keV)	Eɣ (keV)	ɣ or X-ray emission prob. (%)
F-18	PET[2]	β+ (97%), EC (3%)	109 m	-	634	511	194%
G-68	PET	β+ (89%), EC (11%)	68 m	-	1899	511	178%
Y-90	β TRNT	β- (100%)	2.67 d	-	2279	-	-
Tc-99m	SPECT		6.01 h	-	-	141, 18-21	89%, 8%
In-111	SPECT	EC (100%)	2.80 d	-	-	245, 171, 26-27, 23	94%, 91%, 15%, 68%
I-123	SPECT	EC (97%)	13.2 h	-	-	159, 27, 31-32	83%, 71%, 16%
I-131	β TRNT	β-	8.03 d	-	606	637, 364, 284	7%, 81%, 6%
Lu-177	β TRNT	β- (100%)	6.65 d	-	497	208, 113	10%, 6%
223Ra	α TRNT	α (100%)	11.4 d	5780	-	296, 154, 354	13%, 6%, 4%

[2] PET (positron emission tomography) is a technique used in nuclear medicine to generate images of metabolic processes in the body. The tool detects pairs of gamma rays emitted by a tracer (a positron emitter), introduced in the body thanks to radiopharmaceuticals. The gamma camera present in the PET device, can detect the couple of gamma produced during the process and the results of these readings are thereafter converted, thanks to an analogic process, in a three-dimensional image of the tracer concentration within the body.

4 Radionuclide calibrators

Radionuclide calibrators (RC) are well-type, gas-filled ionization chambers, used to measure the activity of a radioactive samples (Gabriel Candelaria, 2010).
A *sample*, in this study, is a container (syringes, vials), in plastic or glass, filled with radioactive materials.
RCs are commonly used in NM laboratories to quantify radiopharmaceutical activity prior to patient administration.
This kind of instruments is composed of four different parts: ionization chamber, current-to-voltage amplifier, voltage gain amplifier, and output display.
An ionization chamber is typically made of aluminum, with an inner wall thickness in the range of a few mm. It is an instrument used to measure the number of ions and electrons created by radiation within a medium. It usually consists of a highly-pressurized gas filled container (chamber) positioned between two conducting electrodes (the *anode* and *cathode*) to which is applied a voltage potential to generate an electric field inside the chamber itself. The sample, filled with a certain amount of radioactive solution, is positioned in the chamber (Fig. 3) that typically presents a specific holder to hold down the container. When the gas between the electrodes is ionized due to interactions with the ionizing radiation produced by the sample, and or with the chamber walls, the ions and dissociated electrons begin to move towards the electrodes of the opposite polarity, creating, in this way, an *ionization current*. The positive and negative charge is supplied by a high voltage circuit that keeps the voltage on anode and cathode constant (Gabriel Candelaria, 2010) (Fig. 3).

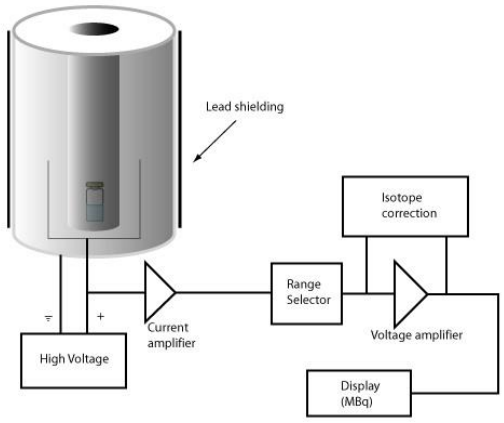


Fig. 3- Ionization chamber block scheme (IAEA, IAEA, s.d.)

The RC operates in the "*full - ionization* " region of the voltage response curve (Fig. 4). In this range, a voltage increase does not affect the number of ion pairs collected and, because this number remains more or less constant, also the generated current can be considered essentially constant.

This phenomenon, called *ionization chamber plateau* (Gabriel Candelaria, 2010), indicates that all the ion pairs are collected without recombination phenomena and that the signal remain constant over the entire range.

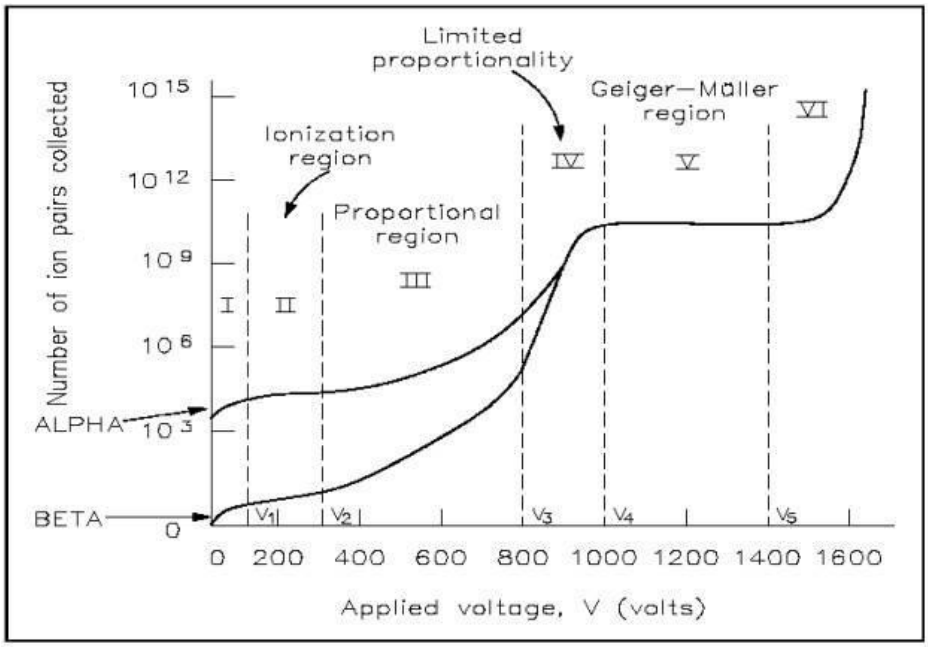


Fig. 4– Voltage Response Curve of the number of the ion pairs collected with respect to the applied voltage (Integrated Publishing, s.d.)

This current is measured by an electrometer circuit capable of performing measurements in the region from femtoamperes to picoamperes. For every ion pair created there is a change in the electric charge of the electrode, thus having a certain proportional correlation between these two parameters or, more simply, between the ion pair generated and the voltage. So, the ionization current can be used as a measure of the ionizing dose entering the chamber and its magnitude is strictly dependent on the amount of radioactivity of the used sample. Because of differences in the types of radiations emitted and their abundance, equal activities of different radionuclides, in general, could generate different current flow (Knoll).

For reading out the correct activity, as is well described in the paper *Dose Calibrator Performance and Quality Contro*l: "the circuit includes a voltage gain amplifier that selects different voltages to drive the output display according to the radionuclide being measured" (Kowalsky, Johnston, & Chan, 1977).

4.2 Factors affecting RC response

RCs are sensitive mainly to photons, which are either emitted by the radioactive source (i.e. gamma rays, X-rays) or produced by interactions with the surrounding media (i.e. scattered photons, X-rays, bremsstrahlung). Charged particles emitted by the radioactive source like beta and alpha particles are usually fully absorbed either in the radioactive solution, in the walls of the container or in the sample holder; thus, in most cases they do not generate a direct current[3] in the ionization chamber. A RC can read the activity of a wide range of radioisotopes.

[3] The response R of the detector to a radioisotope A is defined as the ratio of the detector output to the activity of the radioisotope being measured and it is very convenient to express it relatively to a reference standard radioisotope like is possible to see in the paper "Analysis of a Radioisotope Calibrator" (Suzuki A., 1976).

The current produced by a radioactive source is dependent not only on the energy and abundance of the photon radiation resulting from it, but also on the geometry of the sample (kind of containers, volume of solution inside the container…). For this reason, the response of the chamber is different for the same activity of ^{99m}Tc (main photon energy of 140 keV) than of ^{131}I (photon energies in the range between 80 keV and 722 keV) (Gabriel Candelaria, 2010) and thus a calibration factor (CF) must be applied to the produced signal.

Specific CFs in terms of current output per unit activity (pA/MBq) are determined by the supplier of the device and should be traceable to a national standard of radioactivity. CFs are used to convert the ionization current (pA) directly into activity (MBq).

They are determined using sources in specific geometries (i.e. specific standard container filled-in with a specific nominal volume of solution), thus establishing traceability only for these specific measurement conditions. However, as mentioned before, the geometry of the sample influences the activity readings: samples measured in RCs are often prepared in geometries different than those used during calibration procedures. Container-specific and volume correction factors can be used to improve the accuracy of RC measurements when using samples in non-standard geometries. In any case, this is not commonly applied in the clinic.

The RC response depends also on the wall thickness variation of the sample container. With the increase of this wall thickness the response is reduced. Generally, the effect of an increase in wall thickness is greater in the case of thinner wall chambers, using radionuclides with a mix between high and low-energy photons. This phenomenon can also occur between containers of the same type that, in this case, are influenced by the tolerance reported by manufacturer. This parameter represents the variation in wall thickness, length or in general in the dimensions that is possible to find in samples of the same brand because of the manufacturing process. For this reason, samples classified like equal could present dimensions value different of a certain amount of mm (within the range of ± a certain value suggested by the manufacturer). This effect is also common in the case of syringes, but, because these are made of plastic and low-density materials, the magnitude of the effect is generally lower. As it is specified before, different containers and volumes produce different geometry and attenuation effects for different isotopes. For this reason, the container types, the volumes, and construction materials affect the CFs, also for the same radionuclide.

For the common medical RCs, it is not common to find CFs that take into account all these variables. Typically, they provide correction at the most for the kind of containers in terms of plastic syringe or vial, suggesting percentages of correction with respect the amount of read activity.

For Fidelis, however, the CFs are provided for almost all the most common geometries and radionuclides used in NM.

The comparison between the activity read using CFs that correct the measurement considering the real condition of the experiments (the radionuclide involved, its geometry in term of kind

of container, the needle where it is used) and the one measured using the RCs commonly available in the hospitals in the same conditions, gives an idea on the distance between the real value of activity and the value measured during the normal working processes.

5 Purpose of the study

From the sections above, it follows that the main issues come from the calibration of the RCs that should be able to provide the correct activities reading, in different geometries (container, volume of solution, position of source) and for different radioisotopes (different photon energies, different abundance of photons…).

Medical radionuclides are most commonly supplied in glass vials to the hospitals or are produced on site where specific device like, for example, ^{99}Mo-^{99m}Tc generator or ^{68}Ge-^{68}Ga generator are available.

The activity in the manufacturer containers or in the elution vials from the generators is measured before each administration to the patient in the RCs available in the hospital. In most cases an aliquot of the radionuclide is withdrawn from the vial with a syringe and, because the activity administered to the patient is the one contained in the final syringe, the standard procedure provides that it is measured again in this step and in this container, before the injection into the patient "both as a confirmatory measurement and as a good quality assurance purposes" (Tyler D. K., 2002).

For all the experiments Fidelis RC is used as reference instrument for determining the true activity. For this reason, in order to have the best possible approximation using this instrument, this study proposes an analysis of the factors that contributes to the generation of uncertainties in activity measurements (position of the source in the chamber, operating temperature, etc.).

Typically, CFs for each radionuclide are provided only for one single source geometry, which is usually unknown to the final user. For this reason, another proposal of this study is to find the uncertainties that can affect the measurement in different geometry and volume conditions, focusing on the most common radionuclides and RCs in NM and trying to obtain result as representative as possible of the clinical conditions.

MATERIALS AND METHODS

1 Measured activity

For the measurement of the activity using the RCs it is necessary to take into account two main factors: the presence of the background radiation (BG) in the environment and the fact that all the radioisotopes used during all the tests decay.

For these reasons, all the measurement performed directly using the RCs are subjected to a BG correction, three different values of the BG activity (taken without inserting any sample in the RC) are recorded using the different RCs, they were recorded before performing the measurements of the radionuclide activity. An average of these three values is taken and immediately subtracted to the activity directly measured from the RC, the result of this operation is the measured activity net of the BG (A_{m0}).

To perform these BG measurements, it is required that the environment is not subject to any change, so all the sources used during the experiments (when not in use), were correctly shielded for not influencing the BG.

Subsequently the value A_{m0} obtained is corrected for the decay, in order to compare measurements obtained at different point in time using the decay low (formula 4):

$$A_m = A_{m0} * \exp\left(\Delta t * \left(\frac{\ln(2)}{t_{1/2}}\right)\right) \quad (4)$$

Where:

- A_m is the measured activity corrected for the decay [MBq];
- A_{m0} is the activity measured directly from the RC subtracting the BG but before applying the decay correction [MBq];
- Δt = Difference between the time of measurements and the reference time[4];

2 Radionuclide calibrators

During the project RCs from three different manufacturers are tested: Southern and Scientific (Fidelis), Capintec, Inc. (CRC 55-tR, CRC 35R, CRC 15R), and Comecer (VIK 202, VIK 203).

[4] The reference time is a general value normally fixed for all the experiments (with exception of the accuracy tests) as the 12:00:00 of the 01/01/2017. In the case of the accuracy tests, the reference time is the time provided by the manufacturer, for a determinate radionuclide, in which the activity is defined (i.e. for the radionuclide N at the *reference time* hh:mm:ss dd/mm/yyyy the activity is XX, where XX is the activity given by the manufacturer in MBq).

A general overview of the different RCs follows:

- ***Fidelis secondary standard radionuclide calibrator***

The Fidelis Secondary Standard RC is specified to be used as a Secondary Standards Reference Calibrator and allows medical physicists to check the accuracy of other field RCs (NPL, NPL, 2014).

The device comprises an ionisation chamber designed by the National Physical Laboratory (NPL) in the UK, an electrometer and a user interface unit. The ionization chamber is made of thin walls of aluminium alloy, filled with Nitrogen and is maintained under high pressure.

The RC is equipped with a Perspex holder for the correct positioning of the samples during the measurements

"This ionisation chamber is built to the same specifications as the NPL Secondary Standard master ionisation chamber and is tested at NPL for a range of radionuclides before delivery to the customer" (NPL, NPL, 2014). The device is calibrated for more than 60 radionuclides and gives the possibility to add manually other CFs. The initial list of CFs is available with the instrument and it can then be used for accurate activity measurements, with full traceability to the UK National Standards maintained by NPL.

This RC presents a list of CFs for more than 50 different radionuclides commonly used in the NM field. For each of this radioisotope, the CF is available for the P6 vial, commonly used to test samples in the past. For a great variety of those radionuclides, the CF is also available for the 10R Schott, type 1+ vial (ISO 2003) (which replaced the P6 in 2000 by suppliers of radiopharmaceutical[5]) and for other different containers (syringes with different needles and different volumes and vials), depending on the predicted use of the isotope.

This RC is installed at the SCK•CEN and, for the purpose of the experiment, was moved to the university hospital of Leuven (UZ Leuven), in a dedicated medical room where all the experiments regarding the study of volumes and geometries for different radioisotopes were performed.

[5] See *Calibration of the NPL secondary standard RC for the new 10R Schott, Type 1+ vials; M. Baker, Applied radiation and isotopes 63, Jan 2005* for more detailed information.

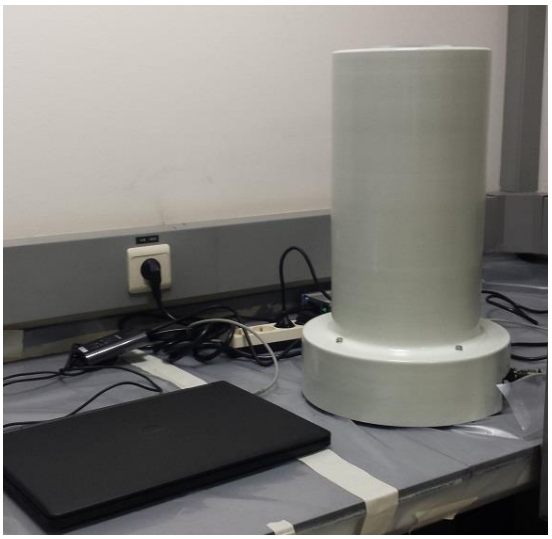


Figura 5 – Fidelis Secondary standard Dose Calibrator

For all the experiment performed, the *vial* used as *reference* is the 10R Schott 1+ vial[6], for which, in Fidelis RC - Southern and Scientific Ltd. (West Sussex, UK) - the CFs are present for almost all the most common radioisotopes used in NM. This vial is a 10 ml glass vial recently used by some of the major suppliers of radiopharmaceutical, for replacing the P6 used until the year 2000 for the distribution vial that for many years has been used for the distribution of a huge amount of radioactive solutions for both diagnosis and therapy (Baker, 2005).

Volume correction Fidelis

The NPL has derived formulas to correct the effect of volume on activity measurements using the Fidelis RC, for many different types of containers. As will be explained later, in this study correction for volume effects was applied when the reference activity concentration of the stock solution used to prepare samples was determined (section 4), and to compare results on the effect of sample's volume on activity measurements from this study with results of volume dependence obtained the volume correction factors determined by the NPL.

The procedure to correct for volume effects using the volume correction factors from the NPL is described below.

In the case of the Fidelis secondary standard RCs, the volume-corrected activity is computed dividing the volume-corrected current by the CF (5) (Tyler D. K., 2002):

$$A_0 = \frac{I_0}{CF} \tag{5}$$

Where I_0 is the volume-corrected current [pA] (6):

$$I_0 = I_m[1 + a_1(m - m_{nom}) + a_2(m - m_{nom})^2] \tag{6}$$

and:

[6] In this work, the activity measurements for all the radioisotopes are always firstly performed in this container using Fidelis RC and applying the CF for the Schott vial 10, and after in all the other geometry and RCs. So, Fidelis RC and Schott vial 10 ml represent the standard of comparison for all the other different geometry.

- I_m is the measured current (corrected for the BG) in [pA].
- m is the mass of solution [g]
- m_{nom} is the nominal mass [g] of the container from the appropriate table (table 2).
- a_1 and a_2 are the volume correction coefficients for the different isotopes and the different containers. These coefficients are in appropriate table.

Formula 6 can also be expressed in terms of activities (7) instead of currents by applying appropriate CF (formula 4) for the source being measured:

$$A_0 = A_m[1 + a_1(m - m_{nom}) + a_2(m - m_{nom})^2] \quad (7)$$

Where:

- A_0 is the activity obtained after volume correction.;
- A_m is the measured activity for a certain volume of mass of solution.

Table 2 - Nominal masses for the 10 ml Schott vial and different syringe sizes.

Container	***Nominal mass (g)***
Schott vial 10 ml	4
Syringe 1 ml	0.1
Syringe 2 ml	0.5
Syringe 3 ml	0.5
Syringe 5 ml	1
Syringe 6 ml	1
Syringe 10 ml	2
Syringe 12 ml	2

As it is specified previously, the nominal mass represents the quantity that can be used inside the containers without applying volume corrections. In this work, for obtaining the correspondent volume in ml the density of every solution is considered equal to 1.

In this case, the CF is different for different volumes of solution inside the container and it does not depend only on the energy of the emitted photons or on the number of emitted photons. So, the CF accounts for the total correction that must be applied on the current to obtain an accurate estimation of the activity.

- ***Capintec RCs***[7]

The *CRC®-55tR's* includes a high-pressure chamber (with ultra-pure Argon at 12 atm) and its reading capability can reach the value of 250 GBq of ^{18}F.

This device present a list of 80 nuclides

When possible, measurements were also performed in two older Capintec RCs used for routine measurements in the hospital.

The *CRC – 15R* RC is an older version of the most recent CRC-25tR. It is an auto-ranging dose calibrator with a list of over 86 different radionuclides. This RC could read until 10^9 Bq of ^{99m}Tc (Capintec, CRC-15R - Radioisotope Dose Calibrator - Owner's Manual, 2007). This is, with *CRC – 35R*, the oldest RCs of the provided by equipment.

All these RCs must be in an environment with a temperature between +10°C and +30°C with a relative humidity up to 90%.

For all these chambers, a Perspex holder is included with a specific hole for syringes and vials. This is inserted in another plastic holder used to protect the ionization chamber from possible contaminations.

For these RCs, it is not possible to choose the CF based on the containers for the different radionuclides, but some corrections are suggested in the manual in the case of syringes. The Calibration Setting Numbers, indeed, are given for 5 g of solution in a standard source ampoule of borosilicate glass (thickness of 0.6 mm). The standard solution in this kind of ampoules is a good approximation for plastic or glass syringes (wall thickness about 1.2 mm) for the majority of the radioisotopes. In general, the attenuation of radiation in a plastic syringe is less than in the standard glass ampoule, while for most of the glass syringes, the attenuation will be greater than for the standard ampoule. For this reason, the value of the activity reading for certain isotopes (computed with the normal calibration factor) must be corrected of a certain percentage expressed in terms of ± X% of the activity reading, where X is a defined number. If the container is a plastic container it is necessary to subtract this percentage from the total amount of activity while in the case of a glass container it is necessary to add it. This correction is applied only to some isotopes like ^{111}In (±10%) or ^{123}I (±15%,).

7 From (Capintec, CRC - 55t - Owner's Manual, 2010), (Capintec, CRC-15R - Radioisotope Dose Calibrator - Owner's Manual, 2007) and (Capintec, CRC 35R - Radioisotope Dose Calibrator - Owner's Manual, 1995)

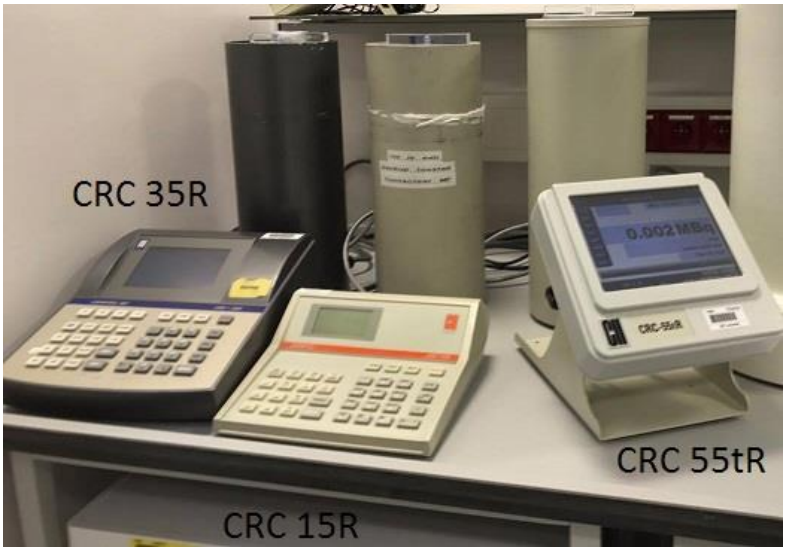


Figura 6 – Capintec RCs available in UZ Leuven in a medical room. From the left: CRC-35R RC, CRC 15R RC and CRC-55tR RC

- ***Comecer RCs[8]***

The *VIK-202* is an Argon filled ionisation chamber with signal processing electronics. The ionisation chamber itself is connected to an amplifier and micro controller board (Veenstra Instruments, 2012).

This RC can read until 74 GBq of ^{18}F. The ionisation chamber's output signal is dependent on the isotope that is measured with it, and the accuracy of a measurement depends on the location, the size, the shape, and the container of the sample to be measured. For these reasons, to take into account these influences, the RC provides height, volume and containers correction for the sample.

In the case of height dependency, the error stays within the 2% for all the isotopes (for a sample measure between 5 and 13 cm above the bottom). For the volume dependency, some percentages of correction are applied for ^{99m}Tc and ^{123}I for different volumes in different containers. For the container dependency, considering that the CFs are extrapolated for thin glass ampoule, the difference between measuring in a glass vial and in a plastic syringe is caused by the attenuation of the low energy gamma/x-ray components of an isotope and by the generated Bremsstrahlung for beta isotopes. For most of the isotopes the error in activity measurements will stay within ± 2 % but for some of them the errors can be much larger, so Comecer provides a list of radionuclides with this correction expressed in terms of ± X%, where X is a defined number, with the same way of application explained for CAPINTEC, Inc. (i.e.: ^{111}In (±10%) or ^{123}I (±15%,)).

[8] From the manuals of VIK 202 and VIC 203 RCs (Veenstra Instruments, 2012) and (Venstra Instruments, 2013)

Fig. 7- VIK 202 in Therapy room, UZ Leuven

The *VIK 203* presents the same characteristics as the VIK 202 but this RC is able to read value of activity until 74 GBq of ^{18}F (Venstra Instruments, 2013).

The volumes correction percentages are in this case provided only by ^{133}Ba (±10%) and for ^{241}Am (±5%).

In general, the most relevant technical parameters are described in the Table 2 for the brands used in this study (the parameter are the same for different device of the same manufacturer):

Table 3 – Most relevant thecnical specification for RCs of the three different tested menufacturers

	FIDELIS	**CAPINTEC**	**COMECER**
Overall accuracy	(*)	± 2%†	± 3 %†
Linearity of measurements	±1%	± 2%	± 1 %
Repeatability of measurements	±1%	±1%	± 1 %
Linearity of pam electrometer	±1%	-	-
Accuracy of pam electrometer	±1%	± 1%	± 1 %

† This is the overall uncertainty stated in the technical specifications of the RCs. However, it is not clear what parameters are included in the uncertainty, nor how it was determined.
(*) Overall uncertainty not specified in the manual. Its value is probably determined mainly from the uncertainty of the CF, the value of which is different for each radionuclide.

While the following table (table 4) shows the CF provided by the manufacturers and their relative uncertainties for all the RCs and all the radionuclides used during the experiments.

Table 4 – CFs and relative standard uncertainties for all the radionuclide used and for the different RCs

Radioisotopes	Schott vial in Fidelis		Capintec*		Comecer	
	CF [pA/MBq]	Rel. std. uncertainty [%]	CF [pA/MBq]	Rel. std. uncertainty [%]	CF [pA/MBq]	Rel. std. uncertainty [%]
^{18}F	10.390	1.10	472	2%	726	n.a
^{68}Ga†	10.320	0.34	416	n.a	749	n.a
^{123}I$	1.721	0.90	277	n.a	618	n.a
^{131}I	4.073	0.40	151	1%	480	n.a
^{111}In§	4.129	0.75	303	1,90	711/696	n.a
^{223}Ra**	3.166	0.38	268	1,65	n.a.	n.a
^{99m}Tc	1.240	0.90	175	n.a	236	n.a
^{90}Y§	0.0721	0.70	480	n.a	902/890	n.a

† For this radioisotope the Fidelis has no CF for Schott 1+ vial. Instead, the CF for P6 vial was used.

$ For this isotope in the case of measurements in VIK-202 with copper filter the CF for copper and syringe and vials are applied. The CF for syringe with copper holder is 145 while the one for vial + copper holder is 106. These CFs were determined by the hospital itself.

§ For Capintec RCs the first CF is in the case of vial the second is in the case of syringe

* For Capintec the CF and the uncertainties are given in an appendix of the manual.

** In this case the CF for Comecer RC was computed by the hospital following the procedure described on the manual.

n.a is not available.

3 Procedure to generate a reference stock solution

The following procedure was followed whenever it was necessary to determine the true (reference) activity concentration of a radioactive stock solution. All activity measurements in this step were done using the Fidelis, which is the instrument used as a reference in this study given its high performance typical of secondary standard instruments. Based on the activity concentration determined with the Fidelis, the true (reference) activity in samples prepared using the same stock solution could be determined using a gravimetric method.

Protocol:

From the vial of the radionuclide supplier the solution is transferred using a syringe to a reference Schott vial 10 ml previously weighted empty (m_e in [g]). The Schott vial is one of the standard containers for which the fidelis has a specific CF and for which the NPL has derived volume correction factors. In this study the reference activity concentration of all stock solutions was determined from activity measurements in this container. If the volume of solution is smaller than the minimum volume for reading the volume corrected activity in the Schott vial 10 ml (*i.e.* 2 ml), then the volume taken from the vial of the supplier is diluted with pure or distilled water to reach at least this amount of solution inside the vial. When this is not

possible (*i.e.* because the container is too big and so the minimum volume to be tested in it is too high; or the number of samples to be prepared from the stock solution are too many), the first minimum volume in the larger samples is reached by adding the stock solution first and then diluting with water directly in the sample. The first activity measurement is performed only after reaching a minimum volume corresponding to the minimum amount of solution that would be measured in the sample container in clinical practice. Such minimum volume depends on the size of the container.

The Schott vial is then measured full (m_{full} in [g]) to obtain the correct amount of the mass solution inside it (m_{ss} in [g]) (8):

$$m_{ss} = m_{full} - m_e \quad (8)$$

The stock solution (SS) activity (A_{ss} in [MBq]) is measured in the Fidelis RC to determine its activity concentration (A_{c_ss}) as (9):

$$A_{c\_ss} = \frac{A_{ss}}{m_{ss}} \quad (9)$$

Assuming the density of the solution is equal to one (water), the activity concentration A_{c_ss} can be expressed in [MBq/ml].

Before of this step, if the Schott vial does not have the nominal volume of solution inside (*i.e.* 4 g of solution equivalent in this study to 4 ml), the correction given from the formula (7) is applied on the measured activity and the activity concentration is computed with this new value of activity corrected for the volume (formula (9)).

The choice of the Schott sample as a reference Sample in the Fidelis RC to determine the correct amount of activity concentration is due to the fact that the fidelis has been calibrated for many radionuclides using this container, therefore many CF are available for this specific standard container. When the CF is not available for the Schott vial, the CF for the P6 vial is used.

The CFs for the Schott vial and their uncertainties for the tested isotopes are listed in Table 5.

Table 5 – CFs [pA/MBq] and relative standard uncertainties [%] for the reference geometry (Schott 10 ml vial) in Fidelis RC for radioisotopes used during the experiment

Radioisotopes	CF for Schott vial in Fidelis [pA/MBq]	Relative standard uncertainty [%]
^{18}F	10.390	1.10
$^{68}Ga^{\dagger}$	10.320	0.34
^{123}I	1.721	0.90
^{131}I	4.073	0.40
^{111}In	4.129	0.75
^{223}Ra	3.166	0.38
^{99m}Tc	1.240	0.90
^{90}Y	0.0721	0.70

† For this radioisotope the Fidelis has no CF for Schott 10+ vial. Instead, the CF for P6 vial was used.

4 Samples preparation

The following procedure was carried out whenever a source sample was prepared from a stock solution.

All the containers of the samples are weighted empty (m_{es} in [g]) before filling with the stock solution from the Schott, and after the filling (m_{fs}). In this way, using the gravimetric method, it is possible to measure the precise amount of solution inside the sample (10):

$$m_{sol} = m_{fs} - m_{es} \quad (10)$$

The syringes are weighed with needle and cap in place, while the vials are weighed with their aluminium cap and the rubber stopper.

By assuming a solution density equal to one, the true activity concentration of the stock solution is then used to determine the true activity A_{true} in the samples by multiplying it by the radioactive volume in the sample (vol_{sol}) (10).

$$\boldsymbol{A_{true} = Ac_{ss} * vol_{sol}} \quad (11)$$

This first filling is the first volume of solution in the sample. If the container to be tested is a syringe, this is filled directly from the Schott vial 10 ml; whereas if the container is a vial, another syringe is used to transfer the required amount of solution inside the sample. Water can be added to reach the minimum volume of solution inside the container necessary to obtain a correct activity reading in accordance with the used CFs (it is known, for example, that in fidelis the CF is corrected for volumes between the 20% and the 80% of the declared volume of the sample).

5 Estimation of measurement uncertainties

Uncertainty due to measurement repeatability

The following calculation procedure was used to estimate the uncertainty due to repeatability of activity measurements.

The standard deviation of the mean, s, and the relative standard deviation, $s_{\%}$, of a set of measurements are determined using formulas (12) and (13):

$$s = \sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{(n-1)}} \quad (12)$$

$$s_{\%} = \frac{s}{\bar{x}} \quad (13)$$

Where:

n is the numbers of measurements;

x_i is the result of each measurement;

$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$ is the arithmetic mean value of the measurements.

Then the absolute standard uncertainty u of the mean (coverage factor k=1, representing a confidence interval of 68%) and the corresponding relative standard uncertainty $u_{\%}$ are derived as follows:

$$u = \frac{s}{x\sqrt[2]{n}} \quad (14)$$

$$u_{\%} = \frac{u}{\bar{x}} \quad (15)$$

Uncertainties in activity measurements using RCs

In this study the following sources of uncertainties were taken into account to estimate the overall uncertainty associated to the determination of the true (reference) activity A_{true} of a sample:

- Short-term variability due to system electronics noise and random nature of radioactive decay. This uncertainty, u_{rep_schott}, was determined from the standard deviation of a set of activity measurements of the Schott vial used to prepare the stock solution, with the vial in the same position (see formulas 13, 14, 15).
- The CFs of the Fidelis for the Schott vial. This uncertainty, u_{CF_schott}, is provided by the manufacturer of Fidelis (see section 3).
- Position of the source in the holder. This uncertainty, u_{pos_Schott}, was determined from the repeatability of consecutive activity measurements placing a ^{137}Cs source in and out of the chamber several times (see section 7.1).

- Measurement of the mass of solution inside the Schott vial used to prepare the stock solution. This uncertainty, u_{mass}, was determined from the tolerance of the balance[9] assumed to be equal to 10^{-4} [g].
- Dimensional tolerances of the Schott vial. This uncertainty, u_{tol_Schott}, was determined from a repeatability test using multiple samples of ^{99m}Tc prepared in a Schott vial (see section 7.3).

The combined relative uncertainty $u_{\%A\_true}$ associated to the determination of A_{true} is, therefore:

$$u_{\%\ A\_true} = \sqrt{u^2_{\%\ rep\_Schott} + u^2_{\%\ CF\_Schott} + u^2_{\%\ mass} + u^2_{\%\ pos\_Schott} + u^2_{\%\ tol\_Schott}} \quad (16)$$

The activity measured with a sample in a given source configuration (A_m) is also affected by similar sources of uncertainty as A_{true}. The combined relative uncertainty $u_{\%A\_m}$ associated to A_m is calculated as follows:

$$u_{\%A\_m} = \sqrt{u^2_{\%\ rep\_sample} + u^2_{\%\ CF\_sample} + u^2_{\%\ mass} + u^2_{\%pos} + u^2_{\%\ tol\_cont\_sample}} \quad (17)$$

where:

- $u_{\%\ rep\_sample}$ is the relative uncertainty determined from the standard deviation of consecutive measurements of the sample being tested (see formulas 12,13,14,15);
- $u_{\%\ CF\_sample}$ is the relative uncertainty due to the CF used to measure the sample. The value provided by the manufacturer was used when available (see Table 4).
- $u_{\%\ mass}$ is the relative uncertainty due to the measurement of the mass of solution in the sample. The same balance was used to measure this mass and the mass of stock solution inside the Schott vial. Therefore, the value of this uncertainty is the same as that used to calculate $u_{\%\ A\_true}$.
- $u_{\%\ pos}$ is the relative uncertainty due to the effect of positioning the sample in the holder of the chamber. The value of this uncertainty is the same as that used for A_{true} for the same parameter in the case of Fidelis. It is not available for the other RCs and for this reason when the activity is measured in these one, this value is null.
- $u_{\%\ tol\_cont\_sample}$ is the relative uncertainty due to the effect of dimensional tolerances of the container used to prepare the sample in the measured activity. This uncertainty is unknown for all clinical containers; thus it was not accounted in the calculation of $u_{\%A\_m}$ (*i.e.* assumed to be zero). This uncertainty was also assumed to be zero when the tested sample was prepared in a Schott vial, in order to keep consistent approach between different samples.

[9] The balance is a Sartorious mod. ME4145 provided by UZ Leuven

As will be seen later, the ratio between A_m and A_{true} was calculated to evaluate the effect of sample geometry (type of container, volume of solution and needle length) on activity measurements using different RCs.

The combined relative uncertainty $u_{\%Am/Atrue}$ of this ratio (A_m/A_{true}) is calculated as follows:

$$u_{\%\ Am/Atrue} = k\sqrt{u^2_{\%\ A\_true} + u^2_{\%\ A\_m}} \tag{18}$$

All the combined relative uncertainties in this study are expressed at a coverage factor equal to 1 ($k = 1$) representing a level of confidence of 68%.

6 Quality control tests

An appropriate quality assurance program is required for the evaluation and the maintaining of the good performance of NM instrumentation. The quality control (QC) of each instrument should have as its starting-point the selection and acquisition of every single instrument, since instruments commonly present different performances (IAEA, Quality Control of Nuclear Medicine Instruments, 1991). After the installation, each RCs has to be checked with a series of *acceptance and routine QC tests*, designed to confirm the manufacturer's specifications and to detect significant change in performance. Acceptance tests should be carried out upon installation of the RC to provide reference (benchmark) data for following routine QC tests.

Different properties should be tested during QC testing of medical RCs, like its linearity, its reproducibility, or its constancy. The recommended frequency for checking each aspect of RC performance is indicated in table 6 (NPL, 2006).

Table 6 – Recommended frequencies for measuring RC performance parameters

	Acceptance	Daily	Monthly	Annually
High Voltage	✓	✓	✓	✓
Display	✓	✓	✓	✓
Zero adjust	✓	✓	✓	✓
Check source	✓	✓	✓	✓
Accuracy	✓			✓
Repeatability	✓			✓
Subsidiary Calibrations	✓			✓
Linearity	✓			✓

The *short-term reproducibility* test consists in assessing the uncertainty coming from the response of the RC when two measurements are performed subsequently. This test is achieved

in our study, using the ^{137}Cs (half-life = 30,17 y) source provided by the Eckert & Ziegler (9.661 MBq at 01/08/2016 12:00).

The *constancy test* (Check source test) gives a measure of the reproducibility of measurements of the ionization chamber (IC) day by day of both the IC and the electrometer. The purpose of this test is to checks the response of the overall system against a benchmark value, established when the system is installed the first time, "to certify the absence of leaks in the pressurized ionization chamber or a progressive drift of the electrometer" (NPL, 2006).

A variant of this test, *the relative response test*, required the use of the same long-lived source used for the test described above, to measure the activity with different CFs, chosen among those of the most common radioisotopes used in NM. Different isotopes needed of different CFs that, as it is possible to notice from formula (5), affect the measurement of activity. The purpose of this test is to check the stability of the system (IC and electrometer) computing the measured current that, for different known value of the CFs and the same source, must be equal in each measurement repeated in the time (weekly or monthly).

The *Linearity test* is performed doing activity measurements along all the activity range of a radionuclide with a short half-life, to check the minimum value until the performed measurements remain in the range of linearity. This test is performed using ^{18}F, with the decaying source method. The measurements can be recorded along a spreadsheet and a log-linear graph made of these measurements plotted against time. The shape of the curve should be straight, showing in this way the dependence on the decay constant: in fact, the slope of the trend line produced for the whole data should be equal to the decay constant of the radionuclide. After a certain number of half-life, it is possible to find a non-linearity region that gives an idea on the minimum value of activity readable from the RC (typically this region is of the order of the background). Predicted activity should be computed using a reference activity, chosen where the slope equates the decay constant, and the decay constant of the radionuclide. Comparing this value with the measured activity during the test, the activity where these two values differ by 1% (reference instrument limit) and 5% (field instrument limit) can then be identified (NPL, 2006).

Accuracy test is performed to test the accuracy of the CFs that are classically provided by the manufacturer. This test must be performed using reference sources, activity of which is traceable to national standards (like 5 ml solution in small glass ampoule (NIST), or a P6/Schott 10 ml vial filled with 4 g (NPL)), in the same reference conditions, for many relevant radionuclides, normally in liquid form. If there is a difference between the container/volume specified by the provider of the calibration source and those routinely used during the normal work conditions of the RCs in the hospital, a subsidiary calibration might need to be performed for the new source geometry, or correction factors might need to be derived for the specific geometry. Normally, these corrections are recommended when the deviation between the activity reading in different geometrical and volume conditions, for example using plastic syringes or different vial with respect to the ones used as reference, and in the standard conditions (isotope-specific geometry and volume) is more than 5%. In this case, after that new

correction factor are determined for these new conditions, it is possible do an accuracy test, during normal routine, to verify their correctness.

The national standard traceability is obtained by purchasing the sources from the National Laboratory or from a secondary standard supplier that can guarantee traceability to the national laboratory for each of the reference source.

6.1 Short term reproducibility

- *Test A*

A set of 10 measurements (10 values of activity) is performed positioning the ^{137}Cs source in the plastic holder without removing it between measurements. Each value of activity and time are recorded. The standard deviation s_{rep_A}, and the absolute standard uncertainty of the mean u_{rep_A} are determined using formulas 12 and 14.

- *Test B*

A similar series of measurements should then be taken removing the source and replacing it in the holder between each measurement. Again, the standard deviation s_{rep_B}, and the absolute standard uncertainty of the mean u_{rep_B} are determined using formula 12 and 14.

6.2 Constancy

This test is performed measuring the ^{137}Cs (half-life = 30y) check source provided by from the manufacturer of Fidelis. This test is performed every day positioning the source in the holder, choosing from the menu of the RC the *check source test* and performing the measurement. The average value is directly recorded in an excel log file. This result is then compared with the activity corrected by time automatically computed from the device. The accuracy of the measurement must be in a range of ±2%.

6.3 Linearity

Linearity test is performed using ^{18}F (half-life =109.77 min, Energy = 511 keV, Photons=193,72) with an initial activity of about 4,4 GBq. The solution was produced directly at UZ Leuven, where a cyclotron is present for the production of this radioisotopes.

The sample is inserted into the holder of the ionization chamber and automatic measurements are performed each 10 min. and recorded in a data log file with other parameters, like the time of measurement, the corrected activity by decay, the background automatic correction and the CF.

The sample remains in the RC for 62 hours, until the radioisotopes reached an activity level lower than the Background measurable activity.

From the data log file, the recorded values are plotted in a log-plot graph with respect to the hours of measurements.

From the results obtained, using the minimum value of activity for which it could be possible to remain in a linearity range, it is possible computing the minimum activity readable by the Fidelis RC, using other isotopes.

This is possible thanks to the linearity between the current and the CF (formula (5)). Using the same value of current corresponding to the minimum activity read in the case of ^{18}F and changing the CF of this isotope with the ones of other isotopes[10], the results is the minimum readable activity for each one of them.

7 Characterization tests

These testes are performed to characterize the response of the fidelis RC as a function of different parameters: ambient temperature, position of the source in the sample holder (x and y axes) and height at which the source is measured (z axis). Additionally, the effect of container dimensional tolerances was evaluated for the Schott 1+ vial.

The first two test were performed using the ^{137}Cs check source available at SCK•CEN, while the others were performed using a source of ^{99m}Tc.

When ^{99m}Tc was used, a procedure consisting in a gravimetric process and an activity measurement was followed to determine the activity concentration in the reference system (Schott vial 10 ml and Fidelis RC) chosen for each specific test. This activity concentration is after used for finding the "true activity[11]" in the samples that is compared with the activity measured. The same procedure is used also for the measurement performed in different geometry conditions and it is explained in the following paragraphs.

7.1 Relative position

Since the response of the RC depends on both the horizontal and vertical position of the source relative to the ionization chamber (NPL, 2006), using the ^{137}Cs check, a *relative position test* is performed to evaluate the uncertainty in activity measurements due to the sample's position in the horizontal plane (sample positioned at the bottom of the holder, in the hole) while a test on *the Response in z axis*, using ^{99m}Tc samples in different geometry conditions, is performed to test how the change in height can affect the activity reading,. To evaluate the uncertainties of these tests the first measurement must be performed in the *normal position* of the sample (position 1, figure 9), depending on the holder, to obtain a reference value of activity for the position that can be compared with the measurements effectuated in the other positions/height steps.

Special holders are provided by the manufacturers to ensure a good reproducibility of source placement inside the RC.

[10] It is possible finding the list of CFs in Fidelis files provided to the installation.
[11] The true activity doesn't represent the real amount of activity present in the sample that is not computable without uncertainties, but the activity that is measured in our standard system of reference.

Fig. 8 – Perspex holder for NPL Fidelis Secondary Standard RC

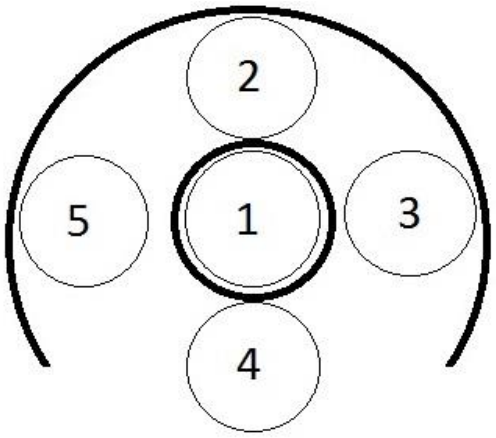


Fig. 9 - Position of the sample in the holder

The activity of a ^{137}Cs check source was measured in 5 different positions (figure 9) of the sample holder provided by the Fidelis RC (Fig. 8). The source was placed in first position and its activity was assayed. Then the holder was taken out, the source was moved to the following position and its activity was assayed again. For all the 5 positions 5 activity measurements were recorded. This process was repeated for all the positions shown in the figure (Fig. 9). The position of the holder inside the chamber was the same for all measurements.

The average activity measured in each peripheral position X (positions 2, 3, 4 and 5) was compared with the average activity measured in the standard central position (position 1). The standard deviation for each set of measurements performed in each position is computed using the formula (12) while the absolute standard uncertainty is measured using formula (14).

7.2 Temperature effect

The *Temperature effect test* is an experiment performed using the ^{137}Cs source, provided by the manufacturer of the RC, to evaluate the change in activity reading performances of Fidelis in different temperature conditions with respect to the normal condition (T between 20°C and 22°C) maintained in the laboratory in which is stored the RC.

The operating environment for Fidelis Secondary standard dose RC is between +5°C and +35°C with a humidity between 0 and 95% (without condensing), and it can be used only indoor (Southern Scientific), for this reason this test is performed in an environment with a temperature between 5°C and 7°C.

This test consists of two different parts and it is performed using the ^{137}Cs check source. The first part (Test A) consists in monitoring the activity changes in a cold room (+5°C) until stabilization while the second part (Test B) consists in monitoring the activity in stable conditions.

- Test A

The entire device (laptop, ionization chamber (IC) and the electrometer) is moved from the room in which it is typically stored to a cold room at ± 5°C.

After the reactivation of the device, three activity measurements are performed each 10 or 15 minutes and directly saved in an excel file to monitor the RC behavior until stabilization.

The test was performed for 2 hours after reaching the stability condition of temperature.

- Test B

After reaching stability in activity measurements 10 values of activity are recorded and saved directly in an excel file.

During both parts, temperature and humidity level of the room are recorded, while the temperature of the RC is checked with an infrared thermometer.

The variation in response during all the process are finally compared with the normal measurements performed in the stored room of the RC, before moving the chamber in the other environment.

7.3 Effect of container tolerance

The activity measurements can be affected by the different characteristics of the sample, so, to investigate the RC repeatability only, all the other parameters are maintained constant. Nevertheless, even if all the measurements are repeated in the same conditions, they could be different because of the manufacturing tolerance. The *effect of container tolerance test* is performed for this reason. A set of 10 different Schott 10 ml vials is used to measure the activity without changing any other condition (same volume of ^{99m}Tc, same background conditions…). The dimensional tolerances provided by the manufacturer, in fact, describe the difference in dimensions between two identical vials. The intensity of the gamma particles is, indeed, affected by this value, because the attenuation of the gamma is strictly dependent on the dimension of the thickness of penetrated material (19):

$$I(x) = I_0 * e^{-\mu x} \tag{19}$$

The (19) is the attenuation law for a gamma beam of initial intensity I_0. This equation shows how the final intensity of the beam, I(x) is affected by the linear attenuation coefficient, μ, and the thickness, x, of the material that has to be penetrated.

The linear attenuation coefficient, μ, describes the fraction of a beam of x-rays or gamma rays that is absorbed or scattered per unit thickness of the absorber, expressed in [m^{-1}].

The 10R Type 1+ Schott vial has an inner layer of pure silica projected for minimizing activity absorption. Measurements carried out at NPL for ^{201}Tl – the radionuclide most prone to adsorption – confirmed the effectiveness of this coating (Baker, 2005). The total height of the vial (h_1 in the fig. 11) is 45 mm (±0.5 mm), the diameter (d_1 in fig. 11) is 24 (±0.2 mm) and the thickness (s_1 in fig. 11) is equal to 1 mm (±0.04). The values in the bracket represent the *tolerance* of the measurements.

Fig. 10 - 10R Type 1+ Schott 10 ml vial, plastic and Al caps

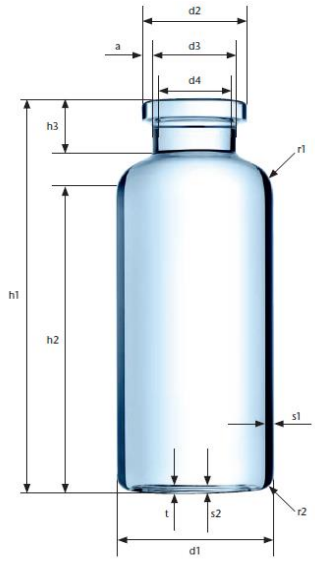


Fig. 11 - 10R Type 1+ Schott 10 ml vial ***(Schott North America)***

This test is performed using ^{99m}Tc (500 MBq, 2 ml of solution, 250 MBq/ml), from the Hart Hospital of Mol, eluted in a 10R type 1+ Schott vial 10 ml.

The initial volume of solution is diluted with distilled water[12] up to a volume of 7 ml, reaching an activity concentration of 71 MBq/ml[13]. This is the stock solution for the experiment. This step is necessary to test 10 Schott vials with the same amount of solution and therefore of activity inside.

All samples are prepared using these same geometry conditions, to avoid the possibility that other changes (for example in the volume) would affected the measurements. The aim of the test, in fact, is to obtain the uncertainties coming exclusively from the manufacturing tolerance that can affect similar samples. If changes in volumes or in other conditions (like for example the background activity in the room) affect the measurements, the obtained uncertainties will no longer be only dependant on the tolerance.

All the activity measurements in this test are performed in the Fidelis RC, using the ^{99m}Tc CF for the Schott 10 ml vial. The first step consists in filling all the samples with the same amount of stock solution, using a syringe. All the containers are measured empty and then fulfilled of solution to obtain the correct amount in gram of radioactive solution present inside.

Having the activity concentration in the stock solution and multiplying it for the volume of radioactive solution in each sample, it is possible to obtain the true activity in each sample.

The minimum volume for a correct reading of the activity using the Schott vial is 2 ml, for this reason all the samples are filled with water until this volume is reached.

[12] In order to maintain the same value of initial activity, changing only the activity concentration.
[13] The amount of solution inside the sample is measured with a gravimetric process: the vial is measured empty and after the filling in order to have the amount of solution in gram. Measuring the activity with Fidelis and dividing it for the mass of solution it is possible to obtain the activity concentration.

After these steps, the activity is measured in all the samples and corrected for BG and time (see formula 4) and this value is compared with the A_{true} computed with formula (11).

The ratio between these two activities is then compared with the nominal (equal to one) and the difference is plotted on a graph for all the samples in the test.

The uncertainty related to the measurements is determined from the standard deviation of a set of activity measurements of the Schott vial used to prepare the stock solution, with the vial in the same position (see formulas 13, 14, 15).

The combined relative uncertainty associated to the determination of A_{true} is given by formula 16, while the overall uncertainty by formula (18)

7.4 Response in z axis

To test how changes in height can affect the activity reading, an altimeter is positioned next to the chamber with measuring tape fixed around its vertical arm (Fig.12).

Fig. 12 - Altimeter

Along the vertical arm of the altimeter a tong is positioned in a clamp to fix a Plexiglas stick, used as support to position the samples inside the holder. During the test, the chamber is placed exactly under the tong and each sample is fixed to the plexiglass stick with a piece of tape.

During this test, the response of Fidelis is tested using three different samples:

- Eppendorf vial
- 5 ml syringe with a blue needle (G21, length 25 mm)
- 10R Type 1 Schott vial 10 ml

The test is performed using a ^{99m}Tc stock solution provided by Hart Hospital of Mol in a Schott vial 10 ml. The solution is diluted with distilled water in the same container provided by the Hospital and this container is used to perform the test. The volume of stock solution inside the samples is given in table 7.

Table 7 – Tested samples and volumes

Containers	Volume of Solution [ml]
Eppendorf vial 1,5 ml	0.5
5 ml syringe with blue needle	0.5
Schott vial	4.1

In the 5 ml syringe the solution is diluted with distilled water to reach the minimum volume to apply the volume correction factor available in Fidelis for this sample.

The first activity reading is performed positioning the sample into the holder without the stick. The subsequent measurements are made fixing the sample to the Plexiglas stick and increasing the height by 2 cm increment. For each height, a set of three activity measurements and times is recorded. Each of this value is after corrected for the background and the decay, and an average of the corrected values is done.

In this test, the true activity is the activity computed in the stock solution. Also in this case, the same gravimetric process used in the section 2.3.3 to obtain the activity concentration in the stock solution, is applied. From this activity concentration, it was possible to compute the true expected activity in all the samples and this value is compared with the measured activity at each height. The difference between the measured and the true activity is plotted as a ratio between these two measurements with respect to their height in the RC

8 Hospital survey on most common nuclear medicine tools

The radioisotopes are provided to the hospitals directly from the manufacturer in glass vial or, in the case of ^{99m}Tc and ^{68}Ga, they are eluted directly in the hospital where specific generators are available.

Typically, the radiopharmaceutical is administered using plastic syringes, which vary in size and wall thickness depending on the manufacturer. In addition to this, another parameter of influence is the amount of solution in the containers and the different tools that can influence the position inside the RCs (like for example the needles). For this reason, a preliminary study, following the guideline given in the NPL report cirm 56 (Tyler D. K., 2002), is performed to understand the principal differences in the tools used in NM field and the radioisotopes encountered in the hospitals. Based on the results of this study, a questionnaire about the most

relevant aspects for the activity measurements is developed and delivered to the principal Belgian hospitals.

The survey is divided into two main areas: the first part concerns the most commonly used radioisotopes (for both pharmaceutical and therapeutic purposes). The principal questions concern the volumes of solutions used in the vials and in the syringes for each different radiopharmaceutical, in order to understand not only the frequency of use of each radiopharmaceutical but also to have a general overview of all the different kinds of vials and syringes used most frequently; for each container that is used, it is asked the nominal and filling volume.

The second part is a detailed list of questions about the materials listed before, focusing on the needles most common used and their characteristics (length and gouge), and on. the kind of lock between the needle and the syringe, knowing from the preliminary study that the most common connections between syringe and needle are the luer tape, as showed in the picture below (Fig. 13):

Fig. 13 – Different luer taper connections (Simple Diagnostic)

The format of the questionnaire is presented in the APPENDIX I.

Nearly 30% of the contacted hospitals answered to the questionnaire (14/50). From the answers, the most common isotopes, containers, and materials utilized in NM (both for diagnostic and therapeutic purposes) were identified and are listed below:

^{99m}Tc: this isotope is the most frequently used (13/14).

^{123}I is used by 11/14 hospitals.

^{18}F is used by 8/14 hospitals.

^{111}In is used by 6/14 hospitals.

^{223} Ra is used by 6/14 hospitals.

^{131}I is used by 4/14 hospitals.

^{90}Y is used by 4/14 hospitals.

^{68}Ga is used by 4/14 hospitals.

Regarding the most frequently used containers, in the questionnaire one principal brand for the syringes was reported (Beckton Dickinson), and three different manufacturer suppliers for the vials (GE Healtcare, Mallinckrodt and TechneVials). The size and the volume of solution inside

the containers depends on the chosen isotope, the kind of treatment and the formulation of the radiopharmaceutical involved.

The most commonly used needles were BD needles, of which the most ordinary size are 23G for 25 mm of length (blue needle) and 21G for 50 mm length (green needle) as shown in the table 10 and figure 25.

Color of needle	Gauge	Length [mm]
Blue	23	25
Green	21	50

Table 8 – Different needles used to perform the tests.

Fig. 14: Blue (left) and green (right) needles.

9 Source geometry effects

For each isotope to be tested a set of different containers and needle is chosen to perform the measurements of activity in the available RCs.

This test shows the difference in activity reading due to all the parameters (mainly geometric ones) that can affect the measurements, and it aims at obtaining the uncertainties for the different containers for most common isotopes, basing the choice of the material and of the solution to be tested on the result of the survey sent to the hospitals. The activity of each radionuclide solution is measured in syringes of different dimensions and features, selected from questionnaire results from the main Belgian hospitals and compared with the true (reference) activity obtained in the Schott vial 10 ml.

The list of the tested radioisotopes and of the containers is showed in the table below:

Table 9 - Used radioisotopes and different containers for geometric and volume effect test. BD is a brand of syringes: Becton and Dickinson while the abbreviation GN and BN are used to indicate the kind of needle: green or blue needle.

Radioisotopes	Provider	Syringes				Vials	
^{18}F	Cyclotron-produced in UZ Leuven Hospital	BD 5 ml with BN	BD 10 ml with BN	-	-	Mallinckrodt 11 ml	Elution vial 25 ml
^{68}Ga	^{68}Ge-^{68}Ga generator available in UZ Leuven	BD 3 ml with BN	BD 5 ml with BN	-	-	Mallinckrodt 11 ml	-
^{123}I	Sodium Iodide from BEL/LUX GE Healthcare	BD 3 ml with BN	BD 3 ml with GN	BD 5 ml with BN	-	Mallinckrodt 11 ml	-

^{131}I	Iodide injection from GE Healthcare Buchler	BD 5 ml with BN	BD ml with GN	-	-	Mallinckrodt 11 ml	Elution vial 25 ml
^{111}In	Mallinckrodt (Indium Oxinate)	BD 3 ml with BN	BD 5 ml with BN	-	-	Mallinckrodt 11 ml	-
^{223}Ra	^{223}Ra-dichloride from Bayer	BD 5 ml with BN	BD 10 ml with BN	-	-	-	-
^{99m}Tc	^{99}Mo-^{99m}Tc generator from the UZ Leuven hospital	BD 1 ml with BN	BD 3 ml with BN	BD 3 ml with GN	BD 5 ml with BN	Mallinckrodt 11 ml	Elution vial 25 ml
^{90}Y	YCl_3 from Ecklert & Ziegler Radiopharma	BD 5 ml with BN				2 ml V vial from Kimax	

BD refers to the brand of the containers: Becton and Dickinson. The abbreviations BN and GN refer to the type of needles: BN is the blue needle (G 23, length 25 mm) while GN is the green needle (G21, length 50 mm), both are of the type BD microlance. The choice of these two needles derived from the necessity to test some samples in the extreme conditions, especially in the case of the Fidelis RC where a non-specific holder for syringes is available.

For each different chosen radionuclide, the following methodology was used to performing test for geometry effects.

The stock solution is transferred from the vial of the supplier or from the elution vial (case of ^{99m}Tc, ^{68}Ga and ^{18}F) to the Schott 10 ml vial, the reference vial for Fidelis. This process is called *stock solution generation* and the true activity that is determined in the fidelis RC, following the same process as described in the section 3, is used as the reference for comparison with the activity measurement in all the samples and for all the used RCs.

After determining the true activity, a fraction of the stock solution is injected in each sample becoming the first volume to be tested.

Starting from this amount of solution, the volume of the solution inside the samples is increased (*volume effect test*) using distilled or pure water to modify only the volume, maintaining the same value of activity. The volume of water depends on the volume of the tested container; typically, 4 or 5 volumes (corresponding to 4 or 5 additions of water) were tested.

If the volume within the container is varied, the absorption of the emitted radiation by the samples itself changes, as does the geometry with respect to the chamber, causing a change in the current response from the chamber. The corrections that are needed are quantified by

"volume correction factors and these are radionuclide, container, and geometry specific" (Tyler D. K., 2002)

The activity is recorded for the first step (initial volume) and for all the dilution steps in the RCs chosen for the specific isotopes. For each volume step the activity is recorded three times and then was computed for each step like the average of these three measurements.

The results are analyzed in terms of ratio between the measured activity in configuration X (A_m) and the true (reference) activity A_{true} determined from the product between the reference activity concentration and the volume of radioactive solution in the sample (formula 4 in section 1 and formula 11 in section 4). The containers listed in the Table 9 were tested using different volumes of solution.

9.1 Geometry effect tests

The procedures to generate the radioactive stock solution and to determine the reference activity concentration of it follow the same protocols described in the sections 3 and 4.

All the measurements are performed in Fidelis and are repeated, at least, in one Capintec and in one Comecer RC.

For all the RCs, a plastic holder for the samples measurements is provided. These holders can be specific holder for syringes and vial, like in the case of Capintec and Comecer RCs, or plastic holder with a central hole, like in the case of fidelis (Fig.15):

Fig. 15 Different holders for placing the sample inside the RCs. From the left 1. Plastic holder for Comecer VIK 202 RC, 2. Fidelis plastic holder, 3. Capintec plastic holder for CRC-55tR RC

For ^{123}I and ^{111}In, because of the low energy photons emitted by these 2 radionuclides (see Table 1), the measurements of the activity are performed not only with the available plastic holders, but also adding an external copper filter (Fig. 16). The copper shield works like a selective absorber for the low energy X-ray.

Fig. 16 Copper filters for Capintec CRC 55tR, used to test the effect of the copper in the reduction of geometric effect on the sample due to its capacity to absorb mostly low energy photons.

After the activity measurement of the first volume, a defined amount of water is added in the sample, to vary the volume inside the sample, and activity and time are recorded for all the containers in the same RC used for the first measurements, in the same conditions (IE: same holder, same CF). This step is repeated until reaching the last proposed filling volume.

For all the RCs, specific CFs were applied, depending on the isotopes and on the kind of container, when it was possible. When the copper filter is used the usual CF for measurements just with plastic holder was used in order to derive a correction factor to apply when this filter could be opportunely used.

In the Fidelis measurements were made always using the CF of Schott vial in order to see the difference in the RC response when a different container was used.

9.2 Volume dependence: comparison with NPL

Some obtained values from the geometric and volume effects can be compared with the result provided by the NPL report CRIM 56 (Tyler D. K., 2002). In this report, it is possible to find the correction volume constants, parameters a_1 and a_2 in (5), for some of the most common containers and isotopes.

To compare the results obtained from the test performed filling the samples with different volumes, it is necessary to compute the ratio between the nominal current I_0 and the measured current I_m.

The nominal current I_0 is obtained by plotting the measured activity A_m (see formula 4) with respect to the mass of solution m_{sol} then, interpolating these two parameters, a trend line with a behavior as similar as possible to the shape of the data (usually a line or a curve of second degree) and then using the formula of the fitting curve to calculate the value of the measured current I_m for a mass m_{sol} equal to the nominal mass m_0 of the type of container.

The nominal mass m_0 of the different containers used is reported in Table 1.

A_0 is the activity measured when the volume of solution is equivalent to the nominal mass m_{nom}, and is obtained by dividing I_0 by the CF of the radionuclide being measured (formula 5 in section 3):

$$A_0 = \frac{I_0}{CF} \tag{5}$$

Then, the ratio A_m/A_0 is calculated and it is plotted with respect to the difference between the mass of solution inside the sample at measurement x, m_{solx}, and the nominal mass of the sample, m_0 (*i.e.* m_{sol}-m_0). The constants of the first and second order terms of the fitting curve generated from the plotted data (A_m/A_0 *vs* m_{sol}-m_0) corresponds to the volume correction factors a_1 and a_2 obtained from the performed experiment.

Similarly, the ratio A_m/A_0 is calculated again (formula 7 in section 3) but using the volume-correction formula and volume correction factors a_1 and a_2 provided by the NPL for the specific container of the sample, and it is plotted as a function of m_{sol}-m_0 in the same graph. In this way the volume dependence observed in the measurements of this study can be compared with the volume dependence corresponding to the formula of the NPL. As a measure to quantify the difference between results of this study and NPL formula, the ratio between A_m/A_n obtained in this study (SCK•CEN) and A_m/A_0 obtained using NPL formula is calculated at 20% and 80% of filling volume:

$$\frac{SCK}{NPL} = \frac{\left(\frac{A_m}{A_0}\right)_{this\ study}}{\left(\frac{A_m}{A_0}\right)_{NPL\ formula}} \tag{20}$$

The *SCK/NPL* ratio is calculated for each type of container for which volume correction factors are available from the NPL (Tyler D. K., 2002)

10 Accuracy test on supplier vial

This test is performed to test the accuracy of the activity stated by the supplier ($A_{supplier}$) of the radionuclide solution. The reference activity of the radioactive solution was determined with a Schott vial in the Fidelis RC using the methodology explained in section 3 of materials and methods.

An aliquot of solution was transferred to a Schott vial and its activity was assayed.

To check the correct activity in the vial of the manufacturer, as delivered, and the correct activity in the Schott 10 ml vial, it is necessary to consider all the activity remaining in the materials used for transferring the solution (i.e. syringes) and in the vial provided by the supplier of the radiopharmaceutical. So, different activity readings must be performed for each syringe used to transfer the active stock solution from the vial of the supplier to the reference one and in the vial of the supplier itself (Fig.17).

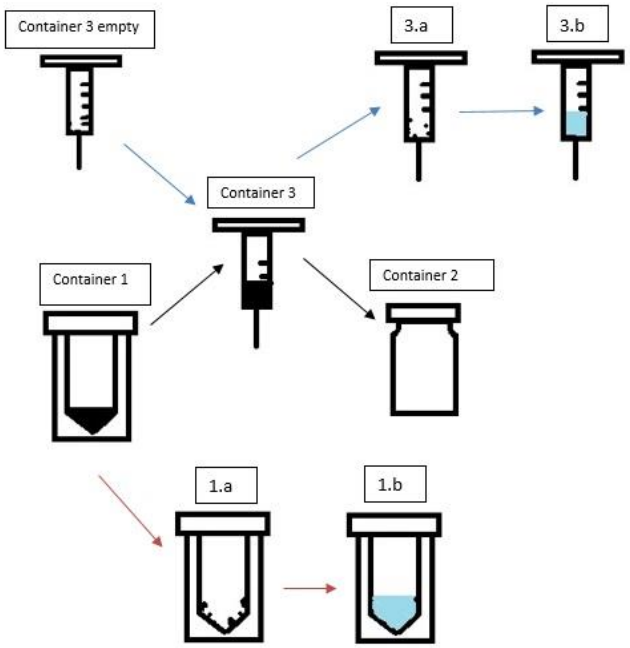


Fig. 17 Accuracy test scheme. From the left: Container 1: supplier vial; Container 3 empty: syringe to pass the solution from the supplier vial to the reference vial; Container 3: syringe filled with solution of Container 1. Container 2: reference vial (Schott 10 ml vial). The path in blue describes the measurements of the remaining activity in the container 3 while the path in red describes the same process for the container 1: containers 3.a and 1.a are the container emptied (after the solution is passed in the container 2 while the containers 1.b and 3.b are the same containers full of water until reach the same volume of solution which previously filled them.

There are two different methods to compute the remaining activity. The first one is mass-dependent (gravimetric method) and the second one is activity-dependent.

The gravimetric method appears more accurate, since the uncertainty in weight measurements is smaller than the uncertainties provided by the repeatability of measurements and the activity readings inside the containers. Knowing the tolerance of the balance, in fact, it is possible to know the accuracy of the measurements, because it is the only parameter that affects the procedure. For this reason, for almost all the isotopes, the activity losses are computed mainly following this procedure.

Referring to the figure 16, all the samples (container 1, container 3 and container 2) are weighed empty and after each transfer of solution (wet). In this way, it will be possible to determine the real activity lost during the entire procedure, considering the proportionality between the activity and the mass itself.

The measured activity of the sample depends on the volume of solution contained. The true activity, indeed, is measured multiplying the activity concentration of the container 2 (that depends on the volume of solution that was possible to transfer from the container 1) for the correct amount of mass of solution remained in the containers 3 and 2. Knowing these masses of solution knowing the true activity concentration, it is possible to compute also the true activity lost in all the used containers.

All the activity measurements are performed using the CF for Schott vial 10 ml for the specific isotopes.

First, the activity of the full container 1 is measured. The second activity measurement is done on the container 3, filled with all the solution of the container 1, and the last one is performed on the container 3, after the filling.

To measure the remaining activity in the container 3 used to transfer the initial solution in the container 2, the wet containers (both the container 1 and the container 3) are filled again with water, to reach the same volume condition of measurement (container 3.b and container 1.b) and to avoid the volume dependence differences in activity reading.

The correct amount of water is determined from the difference in weight between the full container (1 and 3) and the same one in wet conditions (container 1.a and container 3.a) after the extraction of the radioactive solution.

The true activity of the container 1 that is possible to measure at the end of the process is, in this way, given by the sum of the activity measured in the container 2 and the activity lost in the container 3.a and in the container 1.a, because of the remaining solution.

When this procedure is not accurate, like for example using ^{90}Y, for which the mass method could not be used because of the absorption of the radiation by the container plastic wall (in the case of the container 1 and container 3 of the Fig. 16), it is used the activity method.

For both the processes, the quantity that it is possible to obtain through measurements of activities and masses are:

Measured activities in [MBq]

- Container 1 (full and wet): A_{m_supp} (activity of supplier vial when it is full, determined using gravimetric or activity method), $A_{m\_supp\_w}$ (activity of supplier vial when it is wet (after an aliquot of solution has been taken to prepare container 3), measured in Fidelis, Capintec and Comecer RCs);
- Container 3 (full and wet): A_{m_sf} (activity of syringe when it is full determined using gravimetric or activity method), A_{m_sw} (activity of syringe when it is wet (after an aliquot of solution has been taken to prepare container 2) measured in Fidelis RC and Capintec).
- Container 2: A_{m_schott} (Activity in the Schott vial full measure with Fidelis RC determined using gravimetric method, this activity is corrected for the decay and for the volume when the quantity of solution inside the vial is not equal to the nominal value (4g))

Mass of solution [g] (Hypothesis➔ unitary density):

- Container 1 (full and wet): $\mathbf{m_{mf}}$ (mass of full manufacturer container measured during the experiments), $\mathbf{m_{mw}}$ (mass of wet manufacturer container obtained subtracting the value of mass of solution given by the supplier to the mass of full manufacturer container)
- Container 3 (empty, full and wet): $\mathbf{m_{se}}$ (mass of the empty syringe measured at the beginning of the experiment), $\mathbf{m_{sf}}$ (mass of the full syringe, filled with all the possible

extracted solution from the container 1), $\mathbf{m_{sw}}$ (mass of the syringe wet: after an aliquot of solution has been taken to prepare container 2)

- Container 2 – Schott vial (empty and full): $\mathbf{m_e}$ (mass of the empty Schott vial measured at the beginning of the experiment), $\mathbf{m_f}$ (mass of the Schott vial full of solution)

Gravimetric method

True activity in the syringe (A_{true_sf}) can be expressed as the product between the activity concentration of the Schott vial times the mass of solution inside the full syringe (m_{sf}) as expressed in the formula below (formula 21):

$$\boldsymbol{A_{true\_sf}} = \boldsymbol{A_{m\_Schott}} * \frac{\boldsymbol{m_{sf}}}{\boldsymbol{m_f}} = \frac{\boldsymbol{A_{m\_Schott}}}{\mathbf{1}-\frac{\boldsymbol{m_{sf}}}{\boldsymbol{m_{sw}}}} \quad (21)$$

This method considered the proportionality between the mass and the activity, so the amount of activity depends on the mass of solution inside the container. So, computing the true activity in the syringe with formula 22, it is possible to compute the true activity in the wet syringe (A_{true_sw}) as follows (formula 22):

$$\boldsymbol{A_{true\_sw}} = \boldsymbol{A_{true\_sf}} * (\frac{\boldsymbol{m_{ws}}}{\boldsymbol{m_{fs}}}) \quad (22)$$

After having obtained the activity in the wet syringe, the ratio between the mass in the wet manufacturer container and the full manufacturer container is computed to obtain the activity of the container 1.a (formula 23):

$$\boldsymbol{A_{m\_supp\_w}} = A_{m\_Schott} * \frac{(m_{mf} - m_{mw})}{m_f} \quad (23)$$

So, after obtaining the activity remained in the wet manufacturer container and the one in the wet syringe, knowing the activity in the Schott vial, the provided total activity (Am) from supplier is given by (formula 24):

$$\boldsymbol{A_{m\_supp}} = A_{m\_Schott} + A_{mvw} + A_{true\_sw} \quad (24)$$

This activity is compared with the value suggested from the supplier ($A_{supplier}$) in term of percentage of difference (formula 25):

$$\%\ \text{of difference} = \frac{A_{m\_supp} - A_{supplier}}{A_{m\_supp}} * 100 \quad (25)$$

Activity method

The activity of the full container must be expressed in function of the activity of the wet container following the same procedure used for the mass but using the values of activity measured in fidelis during the experiment.

The activity measured in the wet containers (container 1.a and container 3.a from fig. 16), is measured filling the samples with water (container 1.b and container 3.b from fig. 16) until

reaching the same weight that the containers had when full. In this way, the measurement shouldn't be affected by geometry factors.

The activity in the Schott can be expressed as (formula 26):

$$A_{m\_Schott} = A_{m\_sf} - A_{m\_sw} = A_{m\_sf}\left(1 - \frac{A_{m\_sw}}{A_{m\_sf}}\right) = A_{m\_sf}(1 - \mathrm{x}) \tag{26}$$

From this value, considering the ratio $\frac{A_{m\_sw}}{A_{m\_sf}}$ as a constant[14] and calling it $\boldsymbol{x}$, it is possible to obtain the real activity in the full syringe as (formula 20):

$$A_{m\_sf} = \frac{A_{m\_schott}}{(1 - \frac{A_{m\_sw}}{A_{m\_sf}})} \tag{27}$$

From this value it is possible to obtain the value in the wet syringe as (formula 21):

$$A_{m\_sw} = A_{m\_sf} * x \tag{28}$$

The same procedure is made for the supplier vial. So, it is measured the ratio between the activity measured when the container 1 was full and wet ($\frac{A_{m\_supp}}{A_{m\_supp\_w}}$) and it is called y[15]. The value of the activity in the full supplier container (container 1) can be expressed as it follows (formula 22):

$$A_{m\_supp} = A_{m\_sf} + A_{m\_supp\_w} \tag{29}$$

So, knowing the ratio y, it is possible to compute the value of the activity in the full supplier vial (formula 23):

$$A_{m\_supp} = \frac{A_{m\_sf}}{(1-y)} \tag{30}$$

And the value of the activity remained in the wet container (formula 24):

$$A_{m\_supp\_w} = A_{m\_supp} * \mathrm{y} \tag{31}$$

So the total activity in the supplier vial is computed as in the case of gravimetric process (with formula 24 and 25):

$$A_{m\_supp} = A_{m\_Schott} + A_{m\_supp\_w} + A_{true\_sw} \tag{24}$$

[14] The reading of the activities could not respect the effective value of the activity present in the sample, while the ratio between two different value of activity taken in the same sample should be constant in any case (even if the measurements are wrong). In other words, there is a certain stability in the measurements and in the error too.

[15] The reading of the activities could not respect the effective value of the activity present in the sample, while the ratio between two different value of activity taken in the same sample should be constant in any case (even if the measurements are wrong). In other words, there is a certain stability in the measurements and in the error too.

$$\% \text{ of difference} = \frac{A_{m\_supp} - A_{supplier}}{A_{m\_supp}} * 100 \quad (25)$$

RESULTS AND DISCUSSION

1 Quality control tests

The results of the QC tests are presented separately in the following paragraphs.

1.1 Short term reproducibility

Figure 18 showed the tests performed using the ^{137}Cs in Fidelis, making the measurements without removing the source from the holder (orange points), and removing and replacing it (green points):

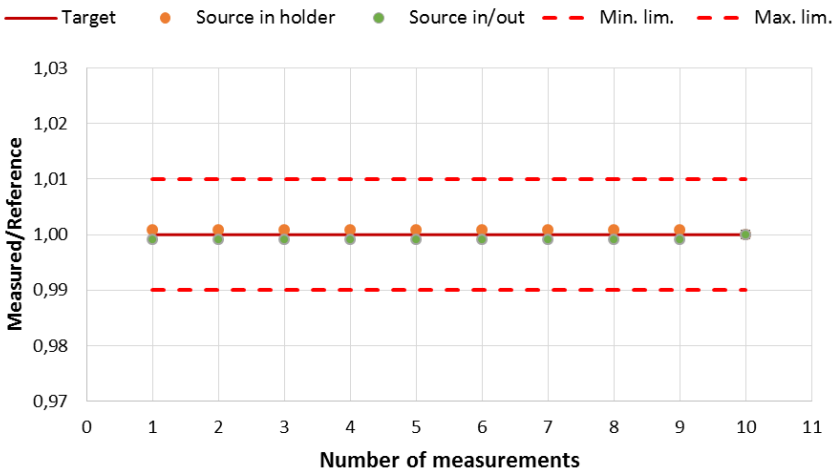


Fig. 18: Short term reproducibility test performed with ^{137}Cs sealed source in Fidelis

The measurements were stable in both cases. The observed variability (standard deviation) from these two sets of measurements was less than 0.5% (the limit of good performance is a relative standard deviation of ≤5%).

1.2 Constancy

The constancy test is accomplished every day. The results of the test are reported in Fig. 19:

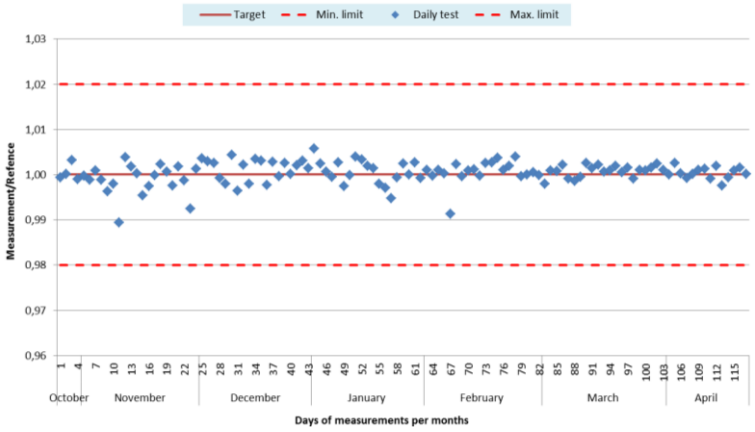


Figura 19 – Constancy test source for Fidelis, using ^{137}Cs sealed source

The readings were within ±2%, which is the limit of good performance set by the manufacturer for this test. Hence the Fidelis has successfully reached the good performance expected for this test.

1.3 Linearity

The result of the test is shown in the figure 19:

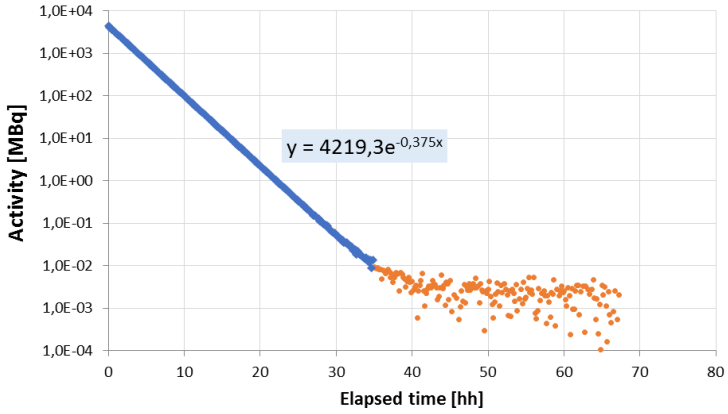


Fig. 20 – Current behaviour with respect to the elapsed time during linearity test using ^{18}F in Fidelis RC. The blue line identifies the behaviour until the linearity is maintained. The dispersion (orange points) represents the recorded activity with a value similar to the BG.

From fig. 20, the linearity was maintained at least until the recorded value started to show an activity of the same order than the BG values (^{18}F activity of about 0.00090 MBq, corresponding to a measured current of 0.009 pA). Of course, from that point on it is not possible to see a linear behaviour (orange data points) because the 18F has almost completely decayed.

From trend line of the blue data points (all data points obtained before reaching an activity level of 0.01 MBq), generating the equation of the decay (formula (4)), it was obtained a decay constant λ=-0,375 and the corresponding half-life of 1,83 h, which is exactly the half-life of the ^{18}F.

The minimum activity that can be measured within the linear range of the Fidelis for different radioisotopes is highlighted in Table 10:

Table 10. Minimum activity readable for different radioisotopes, corresponding to the minimum current measured within the linear range of the Fidelis RC (0.009 pA).

Radioisotopes	^{99m}Tc	^{223}Ra	^{123}I	^{131}I	^{68}Ga	^{90}Y	^{111}In
CFs [pA/MBq]	1.240	3.166	1,721	4,073	10,320	0.0721	4.129
Minimum activity [MBq]	0,0070	0,0028	0,0051	0,0021	0,0008	0,1210	0,0021

2 Characterization tests

The results of the characterization tests are presented separately in the following paragraphs.

2.1 Relative position

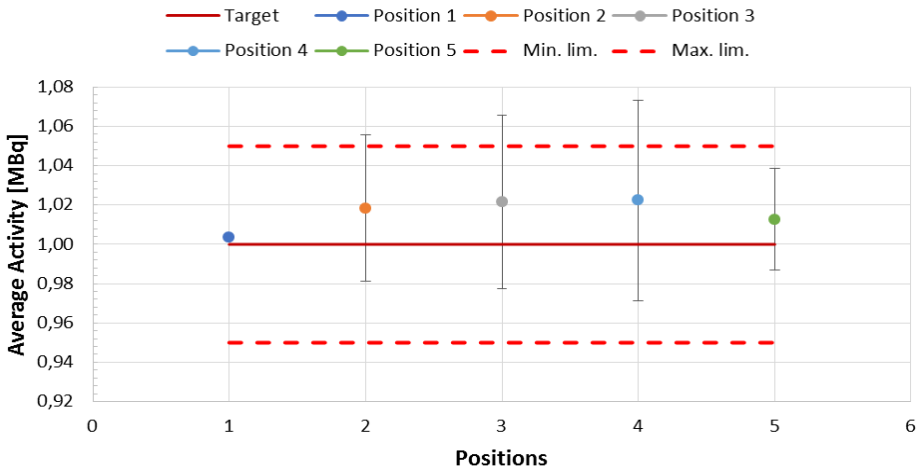


Fig. 21 –Position effect on activity reading using Fidelis RC and ^{137}Cs sealed source

The results of the test are shown in the fig. 21: the reading was most affected by its position in the holder position number 4, where the difference in the measurement with respect the central position (commonly used), were of about the 2%. In all the positions, the computed uncertainties from the repeatability of the measurements were less than this value.

2.2 Temperature effect

- Test A

The temperature behavior and the ratio between the measured and the reference activity, in the cold room, is shown in the fig. 22:

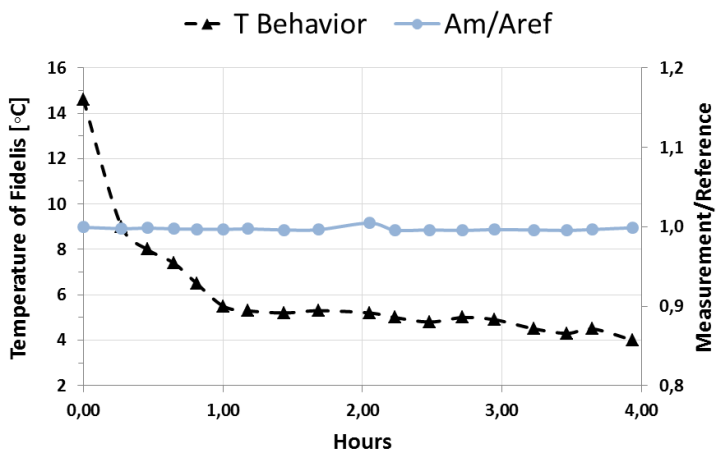


Fig. 22 Temperature behaviour (right vertical axis) and ratio between measured and reference activity (left vertical axis) in the cold room of Fidelis RC, until the stabilization time

From the figure, it follows that Fidelis RC could maintain a certain stability in activity reading for the range of cold temperatures tested, because the measured value of activity is within the range of ±1% of the reference one.

- Test B

The behaviour of the temperature and the ratio between the measured and the reference activity, after the cold room and until reaching stability, is shown in the fig. 23:

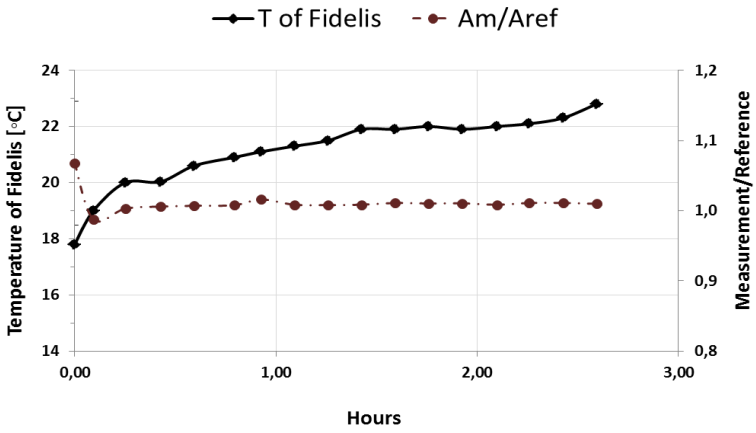


Fig. 23 - Temperature behaviour of Fidelis (left vertical axis) and ratio between measured and reference activity (right vertical axis), changing the position of the RC from a cold room to a normal room (20 – 22 °C)

In this case, because of the faster initial variation of temperature with respect to the one obtained moving the RC in the cold room, the initial activity readings are affected from the environment (measurements in a range of ±6% with respect to the computed activity of the day). The stabilization is obtained only with the stabilization of the chamber at 20°C. These results show how the thermic shock and the consequent increase in temperature can affect the activity reading. The RC, therefore, needed a certain time for the stabilization, which can be approximatively considered as equal to 30 minutes.

2.3 Effect of dimensional tolerance Schott vial

The result of the test is shown in the Fig. 24

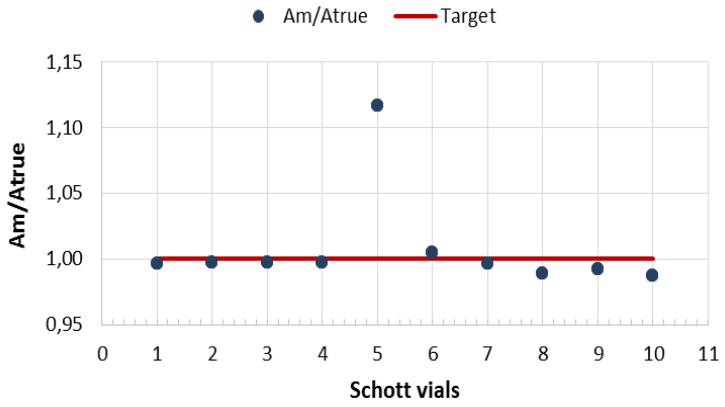


Fig. 24: Ratio between measured and true activity using 10 Schott vials.

From the figure, it follows that the measurements performed in the vials were in the range of ±2% with respect the true activity measured in each one of them with the method described in the paragraphs 2.3.1 and 2.3.2.

Only the measurements performed with the vial 5 gave back a result that is not comparable with the measurements performed with the other vials. Possibly, this result was affected by some human errors and for this reason in the computing of the relative standard deviation (RDS) it was not considered.

So, the RDS of this experiment, without the vial number 5 result, was of about 0,57%.

2.4 Response in z axis

The results are discussed in term of ratio between the activity measured in every position and the true activity computed in the Schott 10 ml vial using the formulas described in the paragraph 2.3.1 and 2.3.2 and are shown in the fig. 25:

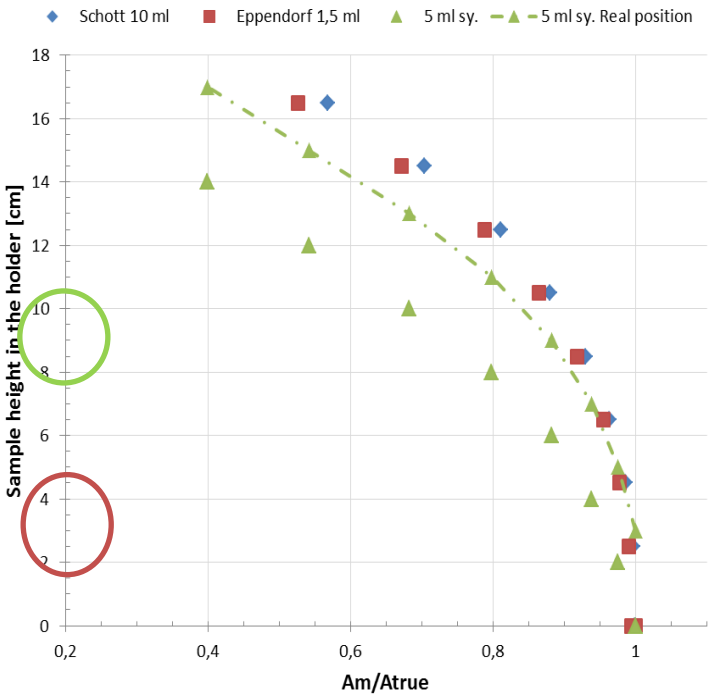


Fig. 25: Activity ratio between measured activity and reference activity with respect to the height of the sample in the Holder, using fidelis RC and ^{99m}Tc for Schott vial 10 (blue), Eppendorf vial 1,5 ml (red) and 5 ml syringe taking into account the real position inside the holder- subtracting the height of the needle (dashed green line) and the height of the measurements with the needle. The green circle indicates the heights in which are performed the measurements for a 5 ml syringe in normal condition, while the red circle indicates the height for measurements performed with a 10 ml vial as Schott 10 ml.

The results of the syringe were highlighted in two different ways: the dashed green line indicated the results of the sample considering the position of the syringe with the needle, while the trend without line referred to the measurement as the substance was in the syringe at the bottom of the holder, without taking into account the presence of the needle (like it was a solid continuous sample, as vial). In this last case, the trend seems to be different but it is only translated on the z axes.

The effect on the Schott 10 ml vial and of the Eppendorf 1.5 ml vial were comparable. For both samples, the measurements performed at the highest position showed an underestimation of the activity reading of more than 40%.

For the syringe the effect is a bit higher probably because this container is longer than the other two and the radiation emitted by the radioactive volume tends to escape earlier than in the other samples where most of the solution is concentrated at the bottom of the container.

From the Fig. 25, indeed, in the case of the real position of the 5 ml syringe (dashed green line) the measured activity was underestimated by about 60% at the highest position (17cm).

In general, it is possible to see that the effect is higher in the last part because the probability of escaping of the radiation is higher with the increasing of the height of the sample. Typically, the measurements are performed between 2-4 cm for the vials (red circle) and between 8-10 cm for the syringes (green circle) and for this height the underestimation of the activity reading is for all the sample around 0% (vials) and 15% (syringe).

3 Source geometry effect

The results of source geometric effect test are divided into two main sections. The first section showed the effect of volumes and materials (containers, needles, filters) for each isotope. The second section showed a general overview of the results of different RCs for a given sample.

3.1 Table of uncertainties

The uncertainties were reported in the table 11:

Table 11 – Relative uncertainties for different radioisotopes

	Radioisotopes							
Uncertainties	**^{99m}Tc**	**^{18}F**	**^{68}Ga**	**^{111}In**	**^{123}I**	**^{131}I**	**^{223}Ra**	**^{90}Y**
$u_{\%mass}$ *	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%
$u_{\%CF\_Schott}$ **	0,90%	1,10%	0,34%	0,75%	0,90%	0,40%	n.a.	0,70%
$u_{\%pos}$	0,03%	0,03%	0,03%	0,03%	0,03%	0,03%	0,03%	0,03%
$u_{\%tol\_schott}$	0,01%	0,01%	0,01%	0,01%	0,01%	0,01%	0,01%	0,01%
$u_{\%CF\_sample}$ **Capintec** §	2%	n.a.	n.a.	1%	1,90%	1,65%	n.a.	n.a.
$u_{\%CF\_sample}$ **Comecer**	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
$u_{\%A\_true}$	0,90%	1,10%	0,34%	0,75%	0,90%	0,40%	0,03%	0,70%

* determined from the tolerance of the balance assumed to be negligible in the computation of the overall uncertainty.
** values indicated by the manufacturer of the Fidelis.
n.a.: value of the uncertainty of the CF not available.
§ values indicated by the manufacturer in the manual

For the ^{68}Ga the CF for the Schott vial 10 was not available and for this reason the CF for the P6 vial was used.

To compute the overall uncertainties for all the radioisotopes must be included the uncertainties for the repeatability of the measurements where all the activity measurements are recorded, that were not reported in this work. So, all the values of uncertainties regarding the measured activities are not reported (there are values for all the volumes measured for all the samples for each isotope), in any case they are in the order of the uncertainties of the CF used to compute

the true activity A_{true} (section 4 materials and methods) or in the order of the uncertainty of the CF for the RC[16].

For all the sample measurements done with Fidelis RC the uncertainty did not exceed the value 1.1% (for ^{18}F), depending on the uncertainty on the CFs highlighted in table 11.

For all the sample measurements done with Capintec RCs the overall uncertainty $u_{\%\,ratio}$ did not exceed the 2.5%. In these cases, the combined relative uncertainty $u_{\%\,ratio}$ depended mostly on the uncertainty of the Fidelis CF for Schott vial 10 ml ($u_{\%\,CF\_Schott}$) and the uncertainty of the CFs of Capintec RCs for the different radioisotopes ($u_{\%\,CF\_sample}$).

For all the sample measurements done with Comecer RCs the overall uncertainty $u_{\%\,ratio}$ did not exceed 1.1%. These RCs did not provide the uncertainty of their CFs. So, the combined uncertainty $u_{\%\,ratio}$ depended mostly on the uncertainty of the Fidelis CF for Schott vial 10 ml.

3.2 Effect of containers

The effect of container type and volume on activity measurements is shown in terms of the measured activity A_m with a given source configuration, and the ratio between that measured activity and the true activity (A_{true}) concentration in the sample, A_m/A_{true}; as a function of the percentage of filling volume. The results are grouped by RCs (this allows a direct comparison of the results obtained with different source configurations).

3.2.1 ^{99m}Tc

Figure 26, 27 and 28 show the results obtained with solution of ^{99m}Tc, grouped per type of container; while Figure 29 shows the same results grouped by RC. The following are the containers and the reference activity A_{true} of the samples tested: 1 ml syringe with BN (24,41 MBq), 3 ml syringe both BN (96,15 MBq) and GN (71,84 MBq), 5 ml syringe BN (99,39 MBq), elution vial 25 ml (103,18 MBq), Mallinckrodt vial 11 ml (50,78 MBq) and Schott vial 10 ml (35,30 MBq). All A_{true} values are specified at the same reference time.

To improve the readability the error bars are not reported in any of the figures. The overall relative uncertainty $u_{\%ratio}$ on the ratio A_m/A_{true} was computed as shown in section 5 of materials and methods (formula 18):

$$\boldsymbol{u_{\%\,Am/Atrue} = k\sqrt{u^2_{\%\,A\_true} + u^2_{\%\,A\_m}}} \tag{18}$$

For ^{99m}Tc $u_{\%ratio}$ was around 1% for Fidelis and did not exceed 2.2% for the other RCs.

[16] These two uncertainties are, more or less, of the same order as it is possible to see from the table 11 and they are between 0 and 2% (^{99m}Tc in Capintec RC).

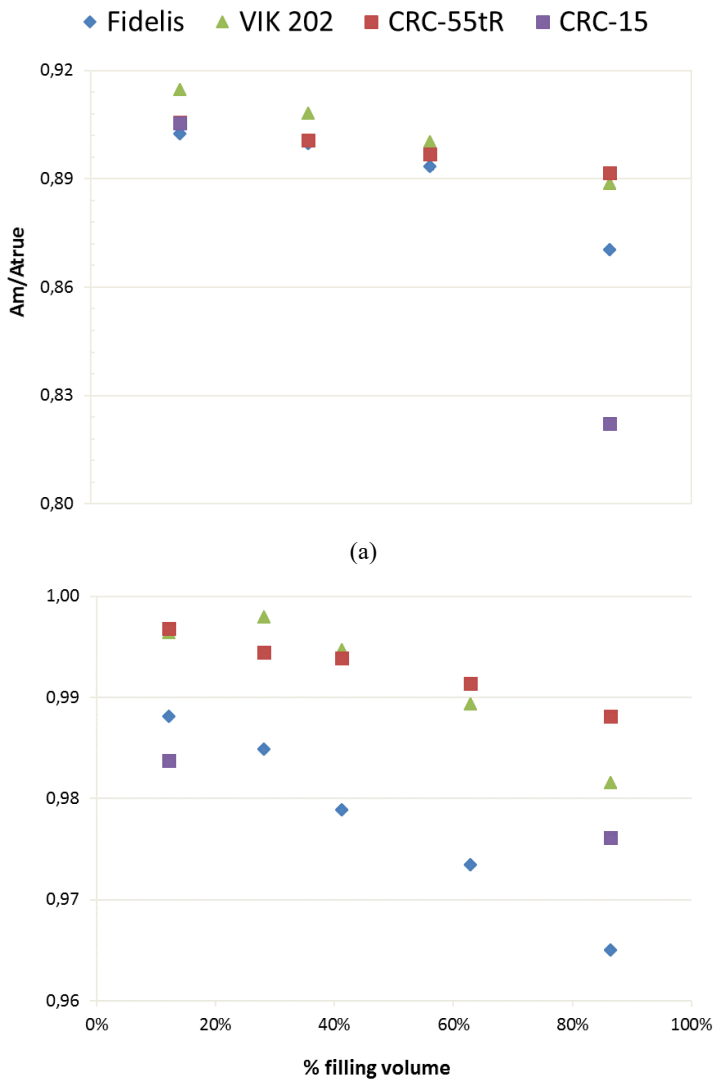


Fig. 26: A_m/A_{true} with respect the percentage of filling volume for (a) 1 ml syringe with BN and (b) 5 ml syringe with BN, filled with ^{99m}Tc.

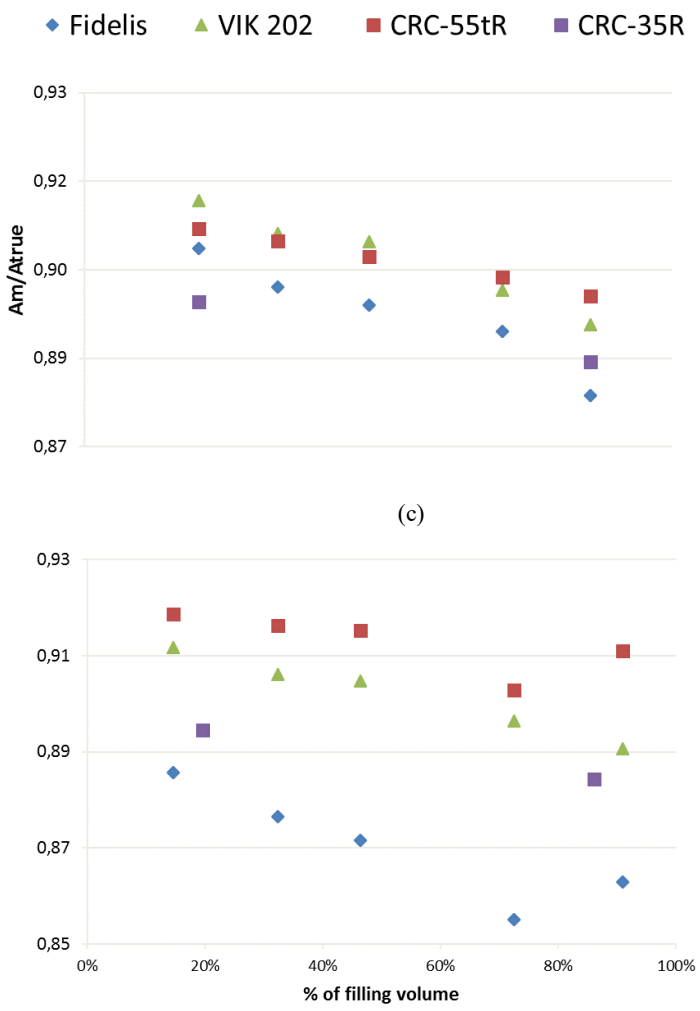
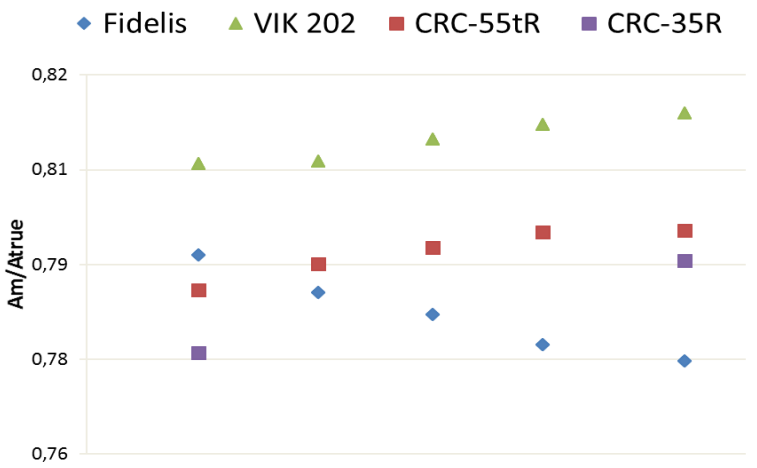
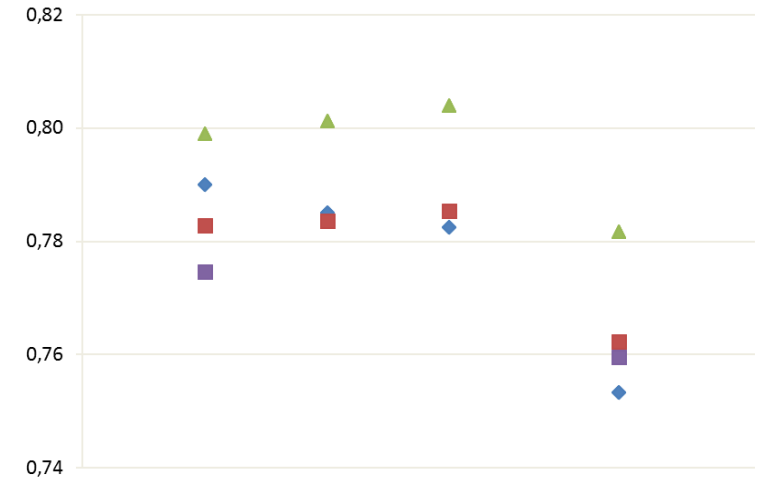


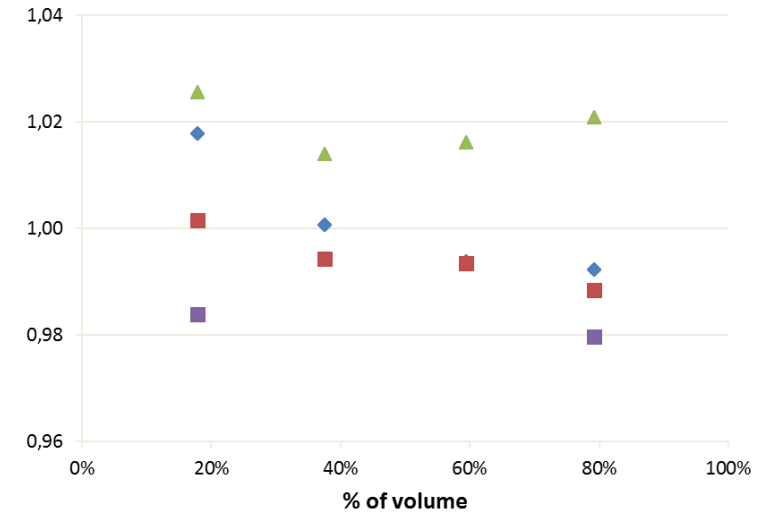
Fig 27: A_m/A_{true} with respect the percentage of filling volume for (c) 3 ml syringe BN and (d) 3 ml syringe GN, filled with ^{99m}Tc



(e)

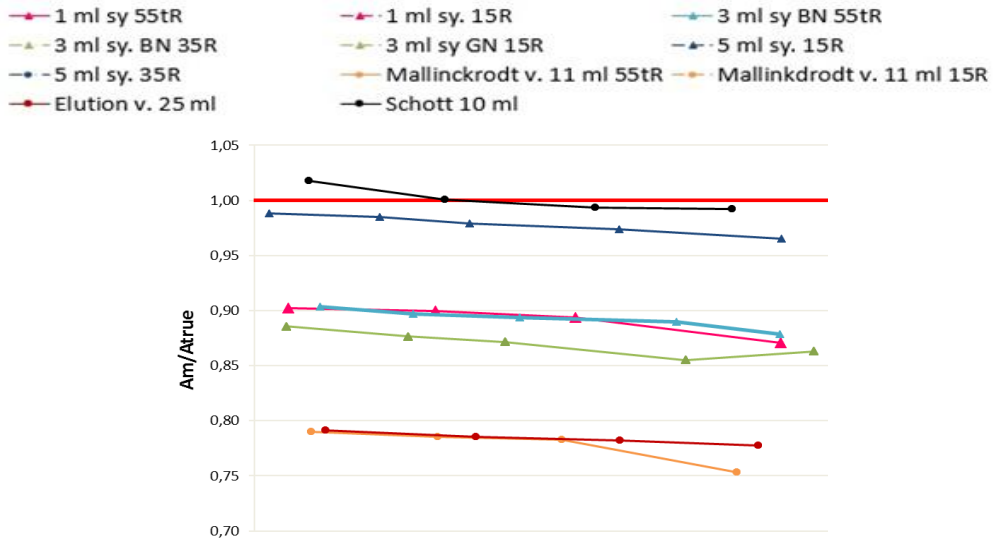


(f)

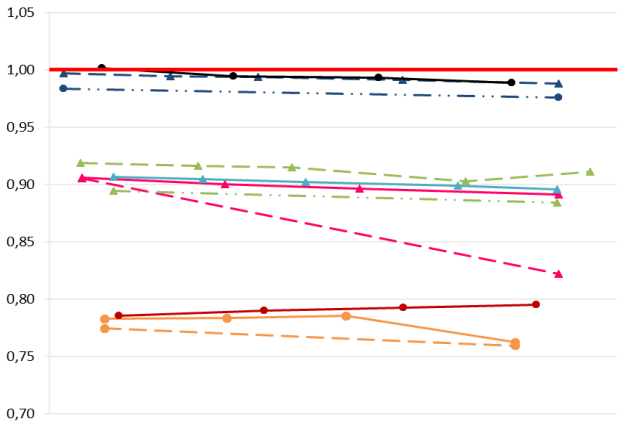


(g)

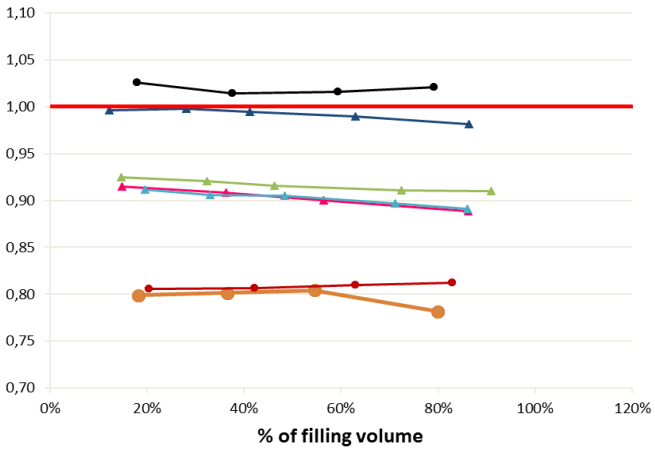
Fig. 28: A_m/A_{true} with respect the percentage of filling volume, for (e) elution vial 25 ml, (f) Mallinckrodt vial 11 ml and (g) Schott vial 11 ml, filled with ^{99m}Tc.



(a)



(b)



(c)

Fig. 29: A_m/A_{true} with respect the percentage of filling volume, for a) Fidelis, b) Capintec (CRC 55tR, CRC 35R, CRC 15R), c) Comecer (VIK 202)

The values of measured activity for all the RCs showed that the changing in volume of solution produce a difference in activity reading within [2-5] %, with except for 1 ml syringe (Figure 26 (a)) in Capintec CRC-15R, where this difference was of about 10% (the largest difference). In the other RCs, for 1 ml syringe this difference remained in the order of 5% (Fidelis) and 2% (others).

For the vials (Figure 28), an appreciable volume dependence is observed with the elution vial of 25 ml in the case of Fidelis RC (5% difference between the activity measured with the initial volume and the activity measured with 80% filling); for the other RCs, the difference did not exceed 2%.

For the Mallinckrodt 11 ml vial and the 25 ml vial for elution, the graphs show an underestimation of A_{true} of about 20% for all the RCs (figure 29). All the other samples showed an underestimation mostly between 10% and 15%, except the 5 ml syringe and the Schott vial for which A_m is always within ±5% of A_{true}. Because of the low energy of ^{99m}Tc photons, glass vials tended to absorb more the radiation in this range of energies, and hence might affect the capability of the RC to read activity. To determine if this underestimation was due to the higher attenuation of photons with the glass clinical vials than with plastic syringes for the lower energies, using formula (19) and the mass attenuation coefficients and densities of glass (assumed to be borosilicate glass) and low-density polyethylene (LDPE) (approximation of the syringe material), an approximation of the attenuation caused by these two materials was computed, for a photon energy of 141 keV, which is similar to 140 keV, the main gamma emission of ^{99m}Tc (see Table 1). The obtained results are shown in Table 12:

Table 12: Attenuation of 141 keV photons (^{99m}Tc) (attenuation coefficient from NIST website: http://physics.nist.gov/PhysRefData/XrayMassCoef/tab4.html) due to container wall thickness of glass vials and polyethylene syringes.

	μ/ρ [cm^2/g] [NIST]	**ρ [g/cm^3]**	**μ [cm^{-1}]**	**Wall thickness x [cm]**	**I(x)/I(0)**
Glass clinical vial**	0.1443	2.23	0.322	0.12	0.962
Glass Schott vial†**	0.1443	2.23	0.322	0.10	0.968
LDPE syringe§**	0.1571	0.93	0.146	0.10	0.985

** The wall thickness of the clinical glass vial is assumed to be that of the P6 vial (0.12 cm).
† The wall thickness of the Schott vial 10 ml is taken from its technical specifications data sheet.
§ The syringes are considered to be made of Low Density Polyethylene (LDPE). The wall thickness of different syringes was measured with a calliper and was more or less constant for all the kinds of syringes used during the experiment.

For the attenuation calculation made in this work, some simplistic assumptions are made:

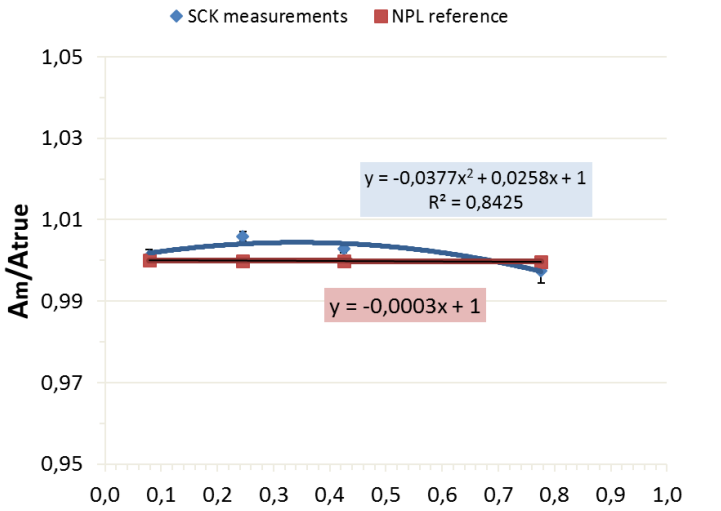
- Monoenergetic beam
- Ideal case with complete absorption
- Each particle is completely absorbed with only one interaction or passes through the medium without change in energy or direction

The difference in attenuation between the three different containers seems to be slightly similar. So, the differences in wall thickness and material between containers does not seem much influence on the attenuation of the main gamma emission, not explaining, in this way, the difference in the results. After an analysis on the low energy photons (around 30 keV) emitted by ^{99m}Tc it was possible to notice that they are almost completely absorbed (only 2% of initial photons are not attenuated by plastic). So, because of this and the low abundance of this low energy photons, it was possible say that they are not the cause of the difference between the containers. Likely, an explanation could be found in the shape of the containers or an incorrect approximation of the glass clinical vial thicknesses.

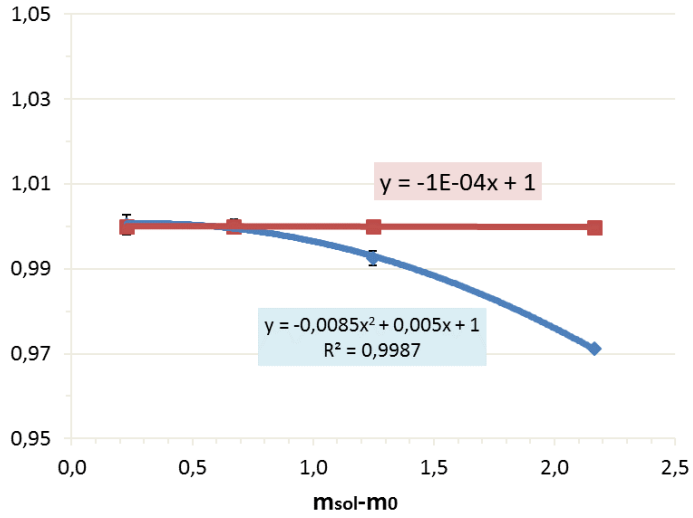
Regarding the effect of needle length on activity measurements of syringe samples, for Capintec and Comecer similar results are observed between the 3 ml syringe with blue needle (BN) and the same syringe with green needle (GN). Instead, with Fidelis measurements of the 3 ml syringe are slightly lower with GN (50 mm length) than with the BN (25 mm). This seems to be due to the different holder designs between Fidelis RC compared to Comecer and Capintec RCs. With Comecer and Capintec holders the syringe is inserted in the specific hole at the upper part of the holder, thus the syringe cap does not touch the bottom of the holder. In Fidelis, the syringes are placed on the bottom of the plastic holder and for this reason different needles influenced the position (height) of the radioactive volume of the sample and hence its activity reading.

3.2.1.1 Comparison with NPL values

Figure 30 and 31 show the results obtained with solution of ^{99m}Tc, grouped per type of container;

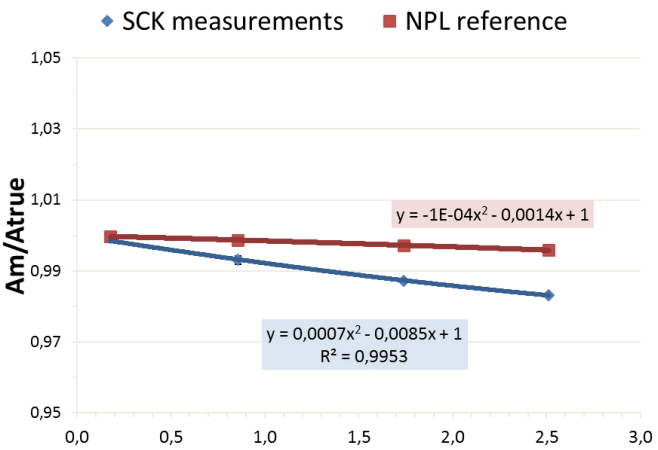


(a)

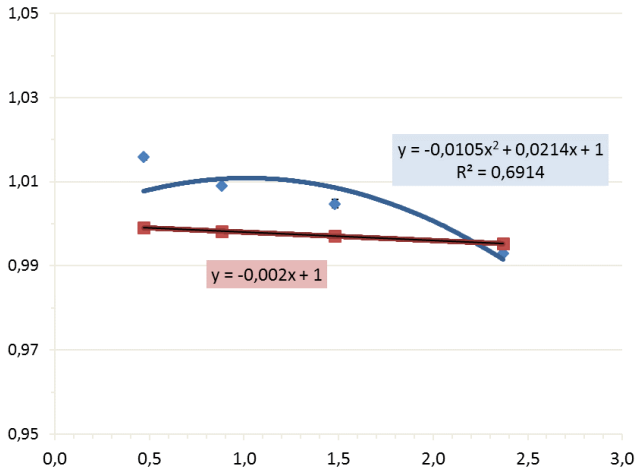


(b)

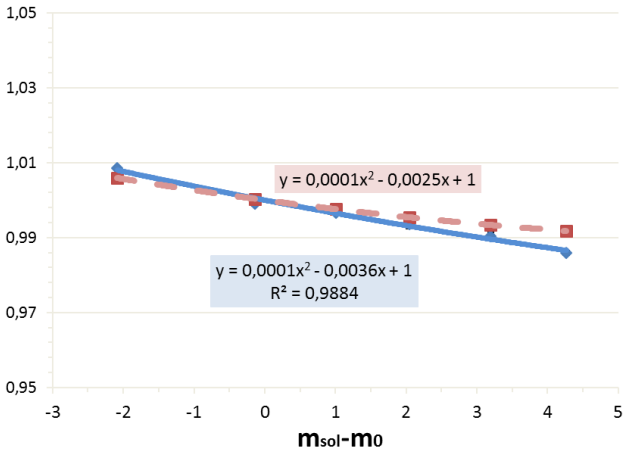
Fig. 30: Graphs of the ratio between the measured activity and the nominal one with respect the difference between the mass of solution for each volume and nominal one for different containers: a)1 ml syringe; b) 3 ml syringe.



(c)



(d)



(e)

Fig. 31: Graphs of the ratio between the measured activity and the nominal one with respect the difference between the mass of solution for each volume and nominal one for different containers: c) 5 ml syringe with blue needle d) 5 ml syringe with green needle e) Schott 10 ml vial.

The difference between the activity measured and the activity of the NPL for the 20% and for the 80% of filling volume was highlighted in the Table 13:

Table 13 : ratio between A_m/A_{true} derived from measurements with the fidelis at SCK•CEN (SCK) and values of A_m/A_{true} calculated using the volume correction factors from the NPL (NPL), for 20% and 80% of filling volume of the different samples.

Containers	SCK/NPL at 20%	SCK/NPL at 80%
1 ml syringe	0,11%	0,22%
3 ml syringe	0,04%	-2,90%
5 ml syringe (BN)	-0,04%	-2,22%
5 ml syringe (GN)	1,68%	-1,38%
Schott vial 10 ml	0,18%	-0,30%

From Figure 29 and Table 13, it is possible to notice that the volume dependence of ^{99m}Tc activity measurements using the Fidelis of SCK•CEN is similar to the volume dependence observed by the NPL for the 6 containers tested. The difference in A_m/A_{true} between SCK and the NPL is within ±0.5% for the 1 ml syringe and the standard Schott vial both at 20% and at 80% of filling volume, and within ±2.9% for the rest of the containers.

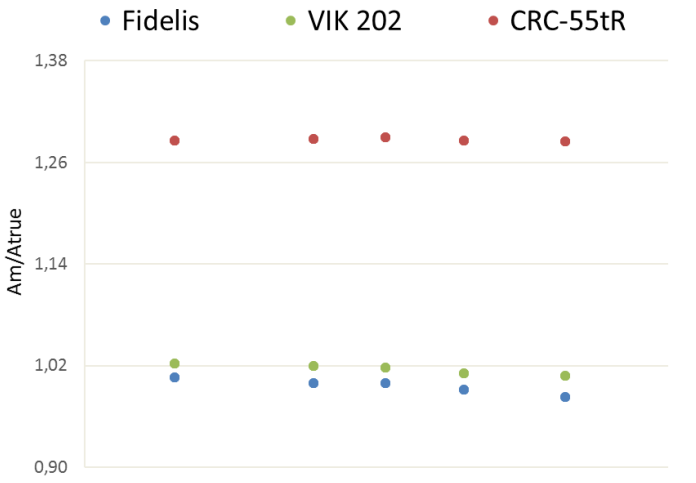
This suggests that correction constants provided from NPL for clinical containers should be used carefully, especially in the case of volumes near to the 80% of the nominal volumes and whenever the activity of a sample needs to be quantified with good accuracy (*i.e.* when the sample is to be used as calibration source to re-calibrate medical RCs).

For example, the measured activity of the 3 ml syringe filled at 80% would be over-corrected for volume if the volume correction factors of the NPL were used. This would increase the error of the estimated activity of this sample.

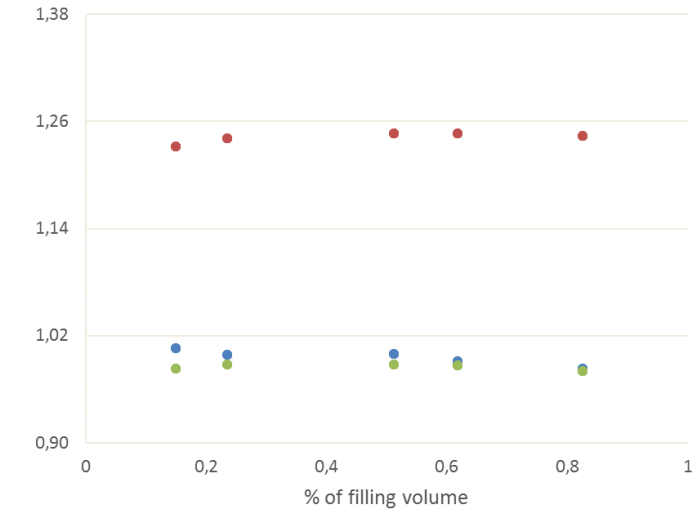
3.2.2 ^{111}In

Figure 32 and 33 show the results obtained with solution of ^{111}In, grouped per type of container; while Figure 34 shows the same results grouped by RC. The following are the containers and the reference activity A_{true} of the samples tested: 3 ml syringe with BN (15,19 MBq), 3 ml syringe both GN (71,84 MBq), 5 ml syringe BN (24,61 MBq), Mallinckrodt vial 11 ml (17,30 MBq) and Schott vial 10 ml (18,26 MBq). All A_{true} values are specified at the same reference time.

To improve the readability the error bars are not reported in any of the figures. The overall relative uncertainty $u_{\%ratio}$ on the ratio A_m/A_{true} was computed as shown in section 5 of materials and methods (formula 18). For ^{111}In $u_{\%ratio}$ was around 0,75% for Fidelis and did not exceed 1% for the other RCs.



(a)



(b)

Fig. 32: A_m/A_{true} with respect the percentage of filling volume for a) 3 ml syringe; b) 5 ml syringe, filled with ^{111}In

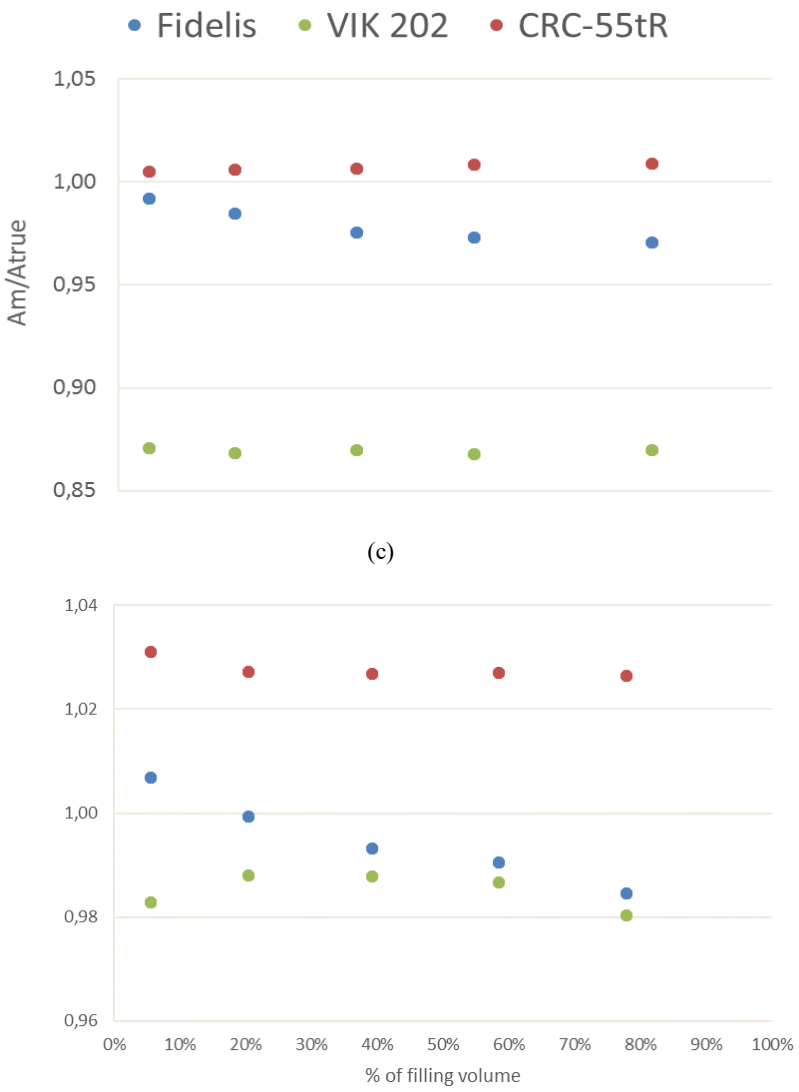
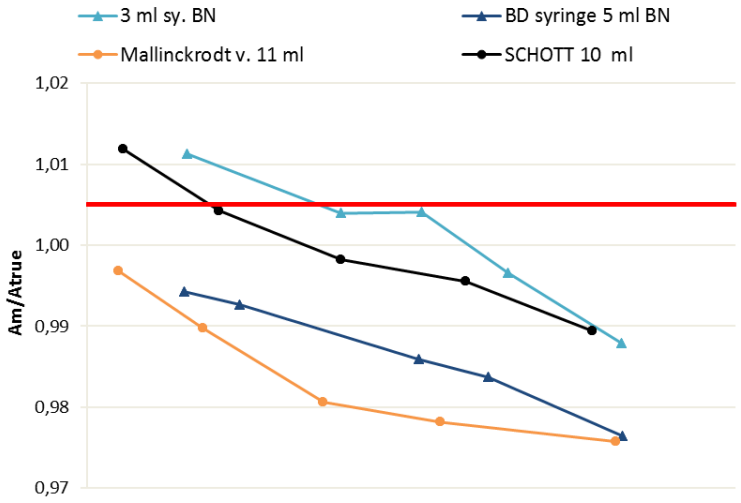


Fig. 33 A_m/A_{true} with respect the percentage of filling volume for c) 11 ml Mallinckrodt d) Schott vial 10 ml, filled with ^{111}In

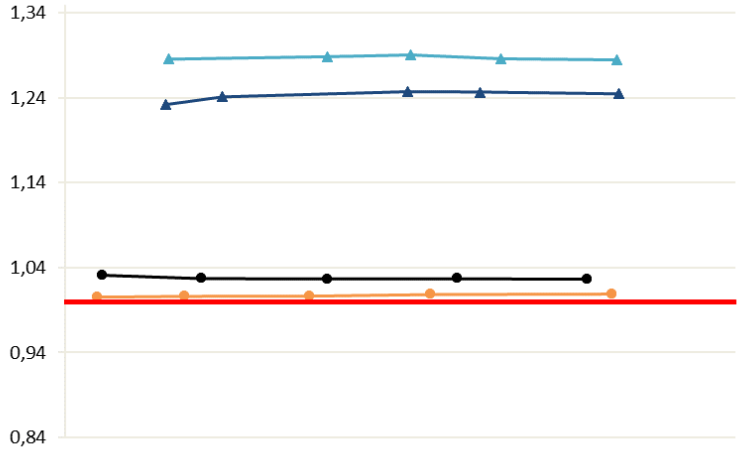
The values of measured activity for all the RCs showed that changes in volume of solution inside the samples produced a difference in activity reading ≤3% for all the samples. For the Fidelis the maximum difference in activity reading between the first and the last volume was 3%; this RC showed the largest volume effect. For CRC 55tR the difference was negligible (around 0,1%) while for VIK 202 this difference is around 1%.

The plots did not contain error bars showing the overall uncertainty. This was, in the case of activity measurement, of the same order as the CF uncertainties for the Fidelis (0,75%) and for the CRC 55tR (1%) while for VIK 202, it was of the same order as the standard deviation. The overall uncertainties on the ratio between measured activity and the true activity was computed as shown in the paragraph 2.5.5.

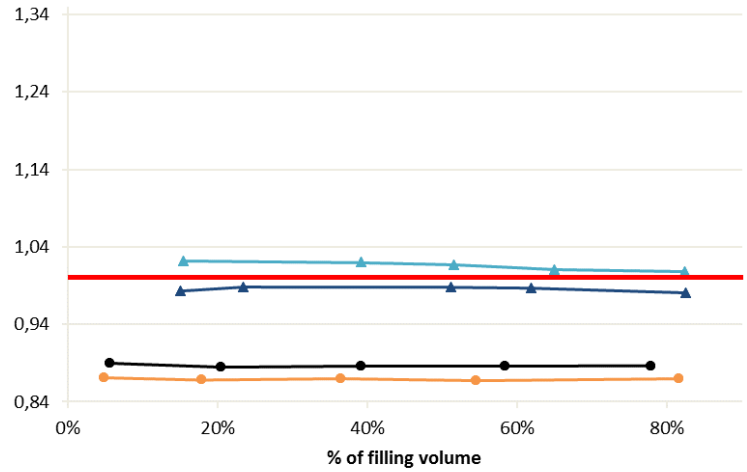
A general overview on the RCs is given in the fig. 34:



(a)



(b)



(c)

Figure 34: ratio between measured activity and true activity with respect the percentage of filling volume for (a) Fidelis, (b) Capintec (CRC 55-tR) and (c) Comecer RCs (VIK 202)

^{111}In presents low energy photons (x-rays of about 23-27 keV with an abundance of 83% per decay). For these energies the attenuation of photons is stronger than in the case of higher energies and for this reason a difference in the attenuation coefficients between different materials and in wall thicknesses can involve a conspicuous difference in the number of photons able to reach the chamber. So, in the following table (tab. 14) it is possible to find the attenuation due to the glass and the plastic in the case of the low energy photons for ^{111}In:

Table 14 – Attenuation of glass and polyethylene in the case of low energy photons (23-27 keV) for ^{111}In.

Photon energy (keV)	Container	ρ [g/cm3]	μ/ρ [cm^2/g]	μ [cm^{-1}]	Wall thickness x [cm]	I(x)/I(0)
20	glass clinical vial	2,23	2,297	5,12	0,12	0,54
	glass schott vial	2,23	2,297	5,12	0,10	0,60
	PE syringe	0,93	0,4315	0,40	0,10	0,96
30	glass clinical vial	2,23	0,7987	1,78	0,12	0,81
	glass schott vial	2,23	0,7987	1,78	0,10	0,84
	PE syringe	0,93	0,2706	0,25	0,10	0,98

The difference in term of attenuation was of about 20% between syringes and vials and this explain the difference activity reading that is possible to see from figures 32, 33 and 34.

On the other hand, the response of the Fidelis is actually similar for syringes and vials (Figure 34 (a)), and A_m values are accurate within ±3% of the reference activity A_{true}. Measurements with the Fidelis seem to be less influenced by the low photon energies emitted by ^{111}In. The low dependence of ^{111}In activity measurements on the type of container with this device could be related to the characteristics of the ionization chamber wall. A chamber with a slightly thicker wall or lining would be more difficult to penetrate by the low energy photons that are not attenuated by the plastic syringe (NPL, 2006), thus the measurement would rely mainly on the higher photon energies emitted by the sample (245 and 171 keV gammas in the case of ^{111}In).

Finally, a similar volume dependence is observed between all RCs: the difference between the first and the last volume is in the range of 2% for Fidelis and in the range of 1% with the other RCs.

3.2.2.1 Effect of copper filter

The activity of all the ^{111}In samples was also measured using a copper filter in the Capintec CRC-55R RC. Measurements with copper shield were done to test if this shield could help to reduce the dependence of activity measurements on the type of container (plastic syringe versus

glass vials, as observed in Figure 35). This material, is used to shield the low gamma radiation of the radioisotopes, limiting geometric influence of the source (these photons are less affected with respect to the high energy photons from the attenuation of the material).

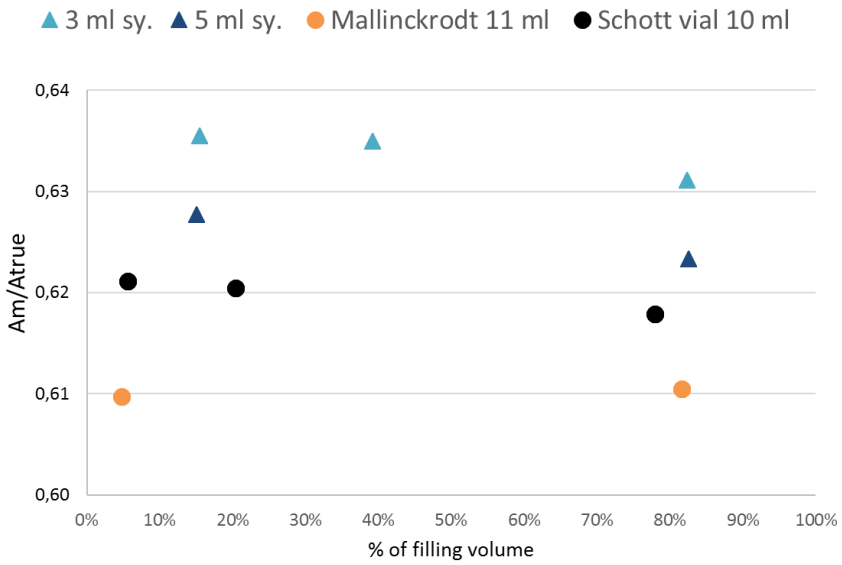


Fig. 35: A_m/A_{true} using a copper holder in Capintec RC (CRC 55tR) for four different containers: 3 ml syringe with blue needle, 5 ml syringe with blue needle, 11 ml Mallinckrodt vial and 10 ml Schott vial, filled with ^{111}In

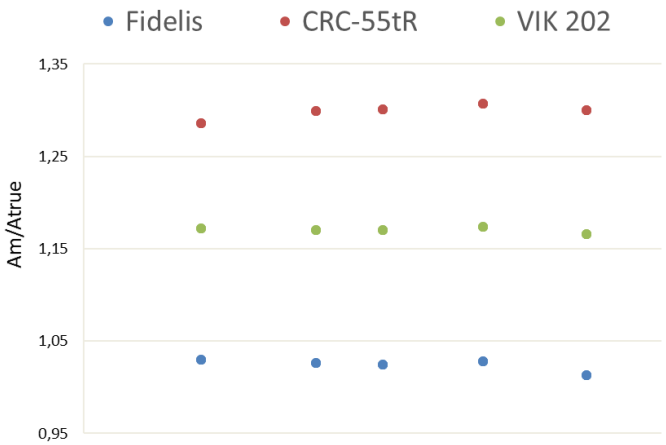
It can be seen in Figure 35 that the ratio between the activity measured and the true activity is similar for syringe and vials. Thus, activity measurements are less dependent on the type of container when the copper shield is used. This is because the copper shields the low energy photons that cause the over-response of the RCs when measuring plastic containers.

All activity measurements underestimated the true activity by about 40%. This is because the CF applied in these measurements was the same used for ^{111}In without considering the presence of the copper shield. A new CF needs to be derived for measurements using the copper shield so that the activity can be accurately estimated.

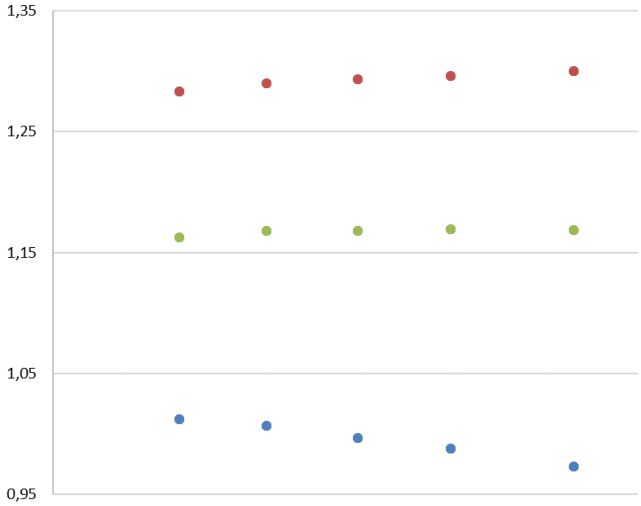
3.2.3 ^{123}I

Figure 36 and 37 show the results obtained with solution of ^{123}I, grouped per type of container; while Figure 38 shows the same results grouped by RC. The following are the containers and the reference activity A_{true} of the samples tested: 3 ml syringe both BN (24,48 MBq) and GN (26,05 MBq), 5 ml syringe BN (33,98 MBq), Mallinckrodt vial 11 ml (83,92 MBq) and Schott vial 10 ml (78,55 MBq). All A_{true} values are specified at the same reference time.

To improve the readability the error bars are not reported in any of the figures. The overall relative uncertainty $u_{\%ratio}$ on the ratio A_m/A_{true} was computed as shown in section 5 of materials and methods (formula 18). For ^{123}I $u_{\%ratio}$ was around 1% for Fidelis and did not exceed 1% for the other RCs.



(a)



(b)

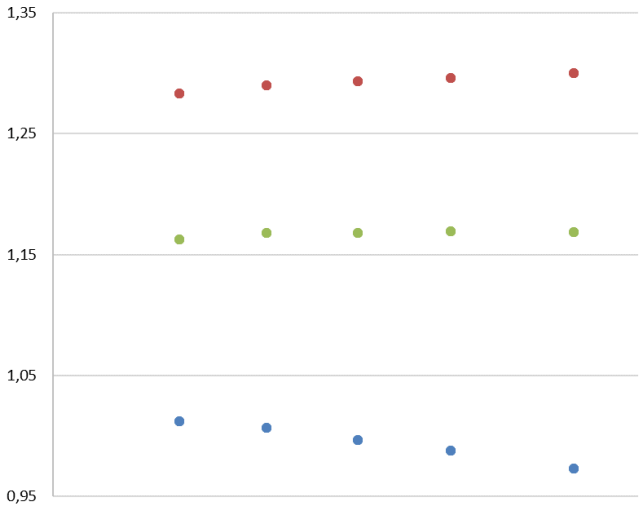
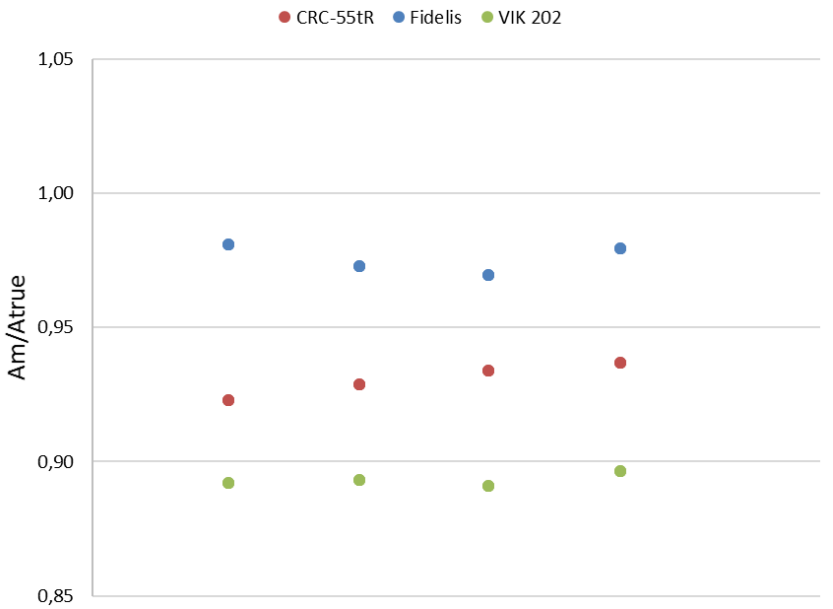
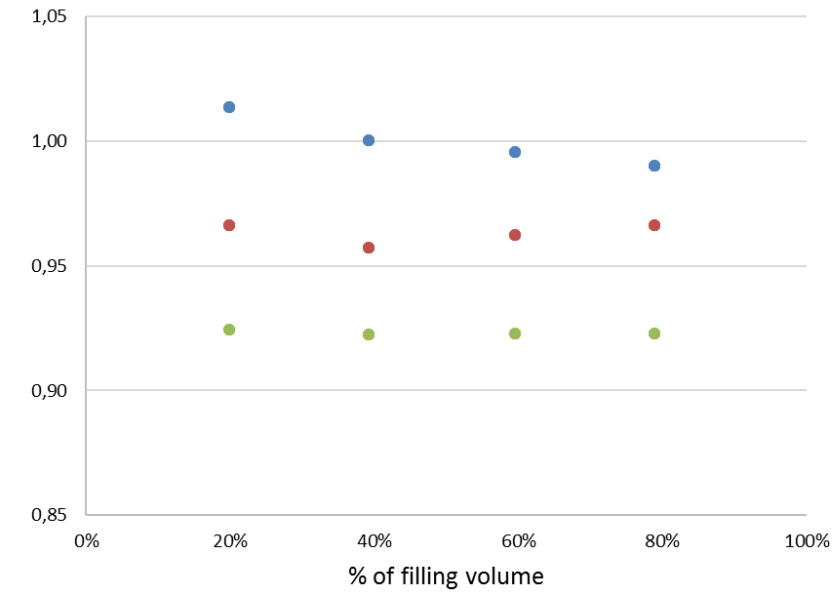


Fig. 36: A_m/A_{true} with respect the percentage of filling volume for a) 3 ml syringe with both blue and green needle and 5 ml syringe with blue needle, filled with ^{231}I

(c)



(d)



(e)

Fig. 37: A_m/A_{true} with respect the percentage of filling volume for d) Mallinckrodt vial 11 ml and e) Schott vial 10 m, filled with ^{231}I

In all the RCs, the changing in volume influenced the activity measurements by a maximum of 2%. The only cases with a difference between the extreme volumes greater than 2% are: 3 ml syringe GN for Fidelis (4%), 5 ml syringe BD (2.4%) and Mallinckrodt 11 (2.2%) ml for CRC 55tR.

A general overview for each RC is shown in the fig. 38:

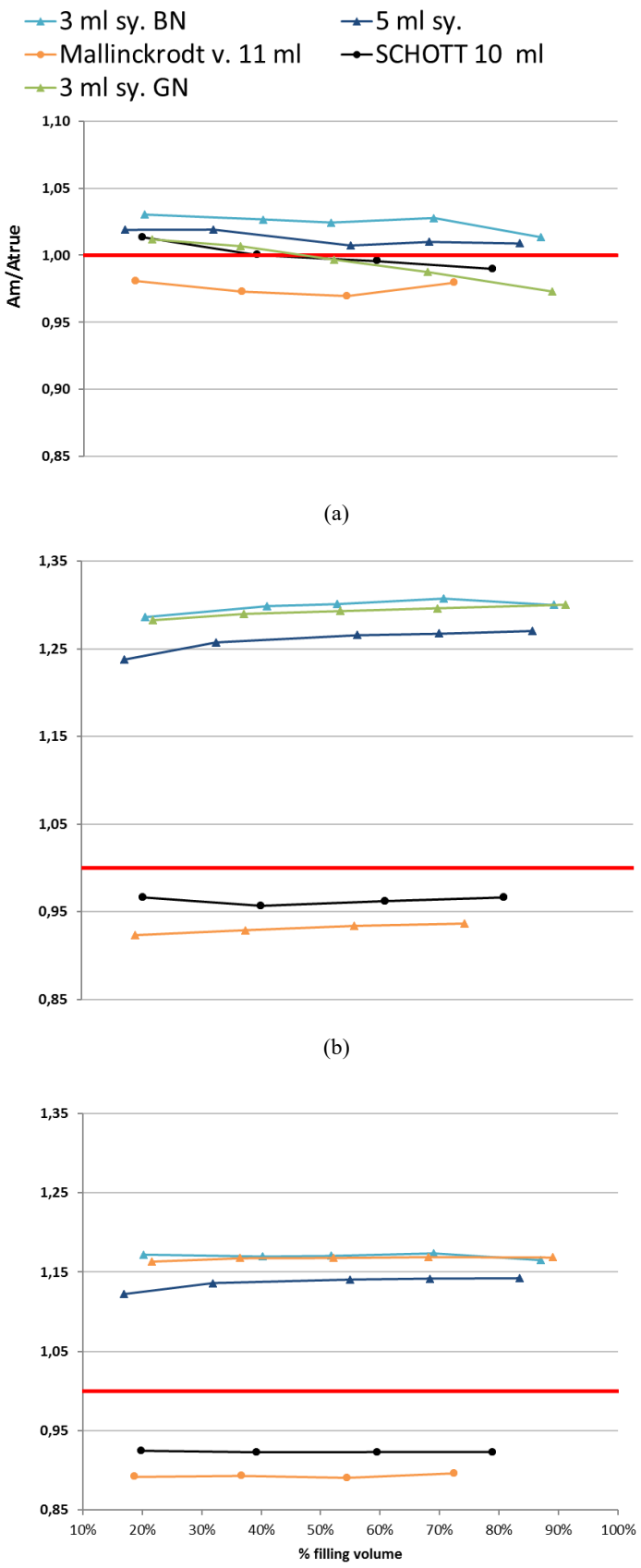


Fig. 38: A_m/A_{true} with respect the percentage of filling volume for a) Fidelis, b) Capintec (CRC 55tR) and c) Comecer (VIK 202) RCs

Both Capintec and Comecer RCs showed an overestimation in syringe activity measurements. The largest overestimation was observed with the 3 ml BD, LL both with green and blue needle (+17% with Comecer and +30% with Capintec). The vials present an underestimation around -5% (Schott vial) to -10% (Mallinckrodt vial) for both CRC 55tR and VIK 202. In general, the response of these clinical RCs is about 30% higher for the syringes than for the vials.

This is because ^{123}I is a low energy gamma emitter and for this reason the CF, that was the same for all the kind of containers and was extrapolated from a thin-walled glass ampoule, tended to overestimate the value of activity read using a plastic container. For both the RCs (CRC 55tR and VIK 202) a correction was proposed in percentage to apply in the case of plastic syringe (chapter 2.1), that for this radioisotope consist of a subtraction of the 15% on the activity reading. Anyhow, from what was emerged from the results of this study it is possible to see that the overestimation of the reading is between 20 and 30% for Capintec and between the 10 and 15% for VIK202.

The reason for the high dependence of activity measurements on the type of container (syringes *vs* glass vials) is because ^{123}I has a high abundancy of low energy photons (characteristic X-rays of 27-32 keV) in its decay scheme. Thus, the same effect observed with ^{111}In samples happens with ^{123}I: these low energy photons are more attenuated by the walls of the glass vials (because of the significantly higher attenuation coefficient of glass than plastic, in particular at low photon energies) than by the walls of the plastic syringe. Therefore, in a plastic syringe more of these low energy photons reach the ionization chamber of the RC, generating a higher response than in the case of glass vials.

On the other hand, with Fidelis there is a certain stability in the measurements of different containers, like in the case of the ^{111}In. The behavior of the ratio between measured activity and the true activity is comparable between all the samples (for both syringes and vials) and is in the range of the ±3% around unit, giving a further confirmation of the fact that the low energy photon emissions affected less this RC with respect the other two.

Regarding the influence of the needle length, the two identical syringes 3 ml BD LL tested with different needles did not show a change in behavior in VIK 202 and CRC 55tR, while for Fidelis they showed a small difference in activity reading in particular at higher filling volumes (at the maximum volume the response is about 4% higher with the blue needle, which is 25 mm shorter than the 50 mm green needle).

The volume dependence for all the samples in all the RCs is very small (≤2%).

3.2.3.1 Effect of copper filter

The same measurements were performed with the use of a copper filter in Capintec CRC-55R RC. The results are shown in the fig. 39:

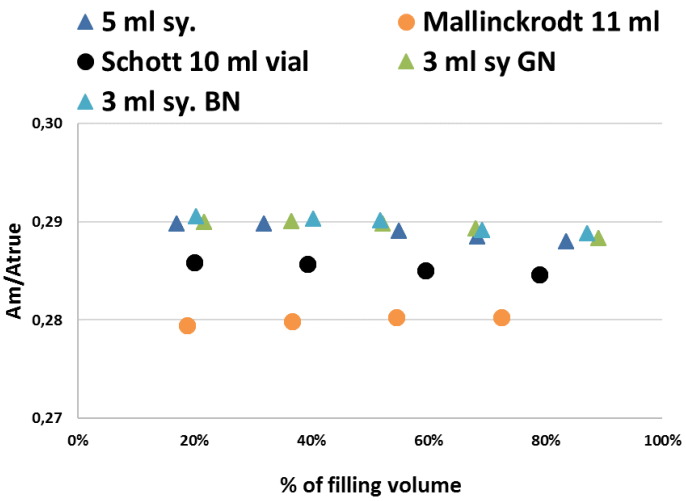


Fig. 39: A_m/A_{true} using a copper holder in Capintec RC (CRC 55tR) for five different containers: 3 ml syringe with both blue and green needle, 5 ml syringe with blue needle, 11 ml Mallinckrodt vial and 10 ml Schott vial, filled with ^{123}I.

The mitigation effect of the low photons is the same explained previously for ^{111}In (paragraph 3.2.2) but in this case, the syringe ratio between the activity measured and the true activity was in the same range of the vials. This meant that the copper has shielded the low radiation, mitigating the container effect that was stronger for material like the plastic (as it was possible to see in the paragraph 3.2.3 (figure 38)).

3.2.4 ^{18}F

Figure 40 and 41 show the results obtained with solution of ^{18}F, grouped per type of container; while Figure 42 shows the same results grouped by RC. The following are the containers and the reference activity A_{true} of the samples tested: 5 ml syringe BN (648,64MBq), 10 ml syringe BN (819,33 MBq), Mallinckrodt vial 11 ml (567,88 MBq), elution vial 25 ml (386,51 MBq) and Schott vial 10 ml (1647,72 MBq). All A_{true} values are specified at the same reference time.

To improve the readability the error bars are not reported in any of the figures. The overall relative uncertainty $u_{\%ratio}$ on the ratio A_m/A_{true} was computed as shown in section 5 of materials and methods (formula (18)). For ^{18}F $u_{\%ratio}$ was around 1,1% for all the RCs.

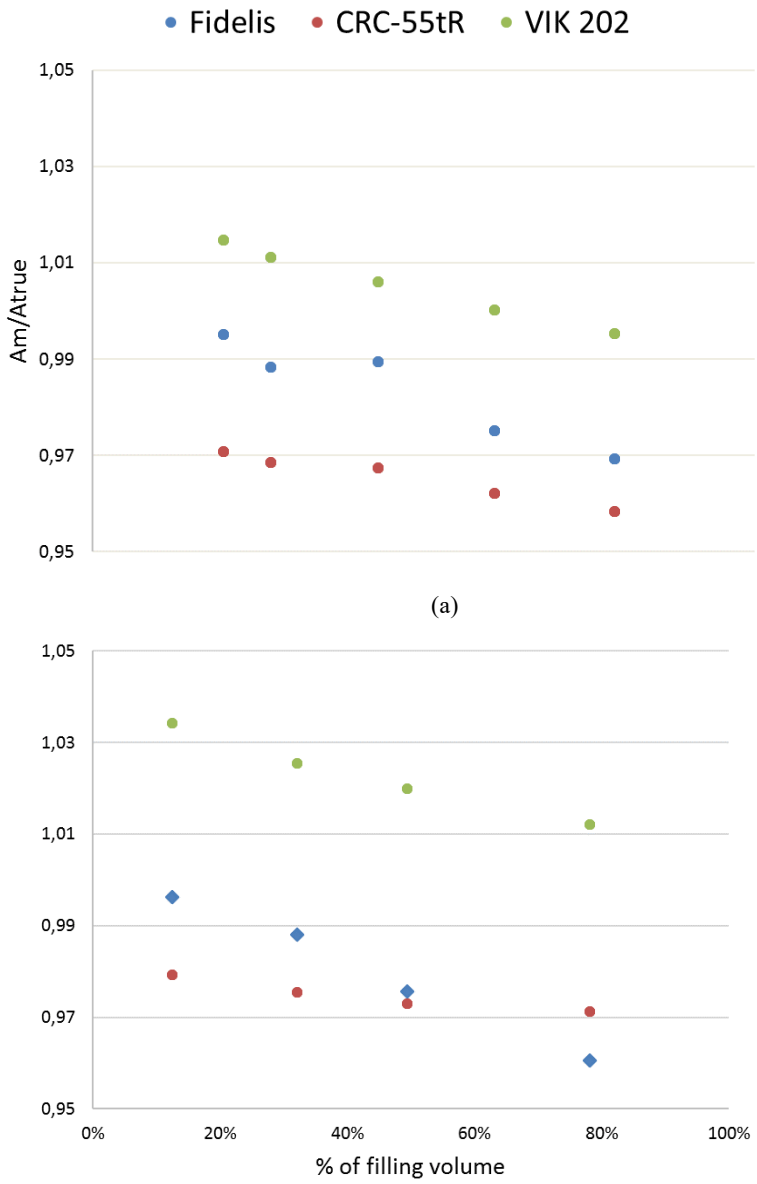
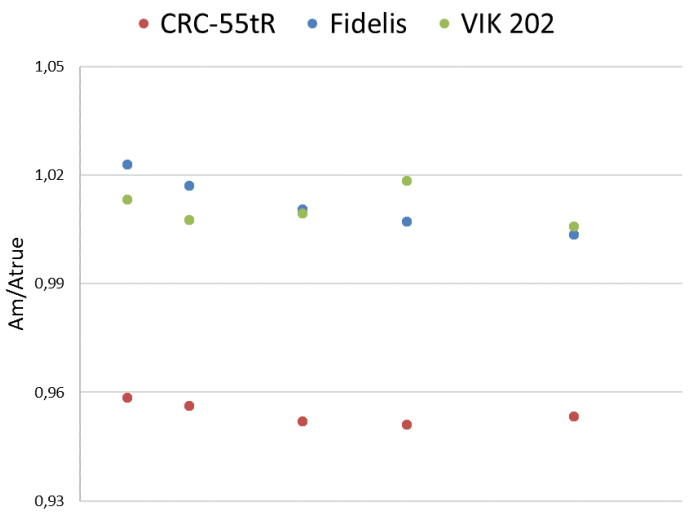
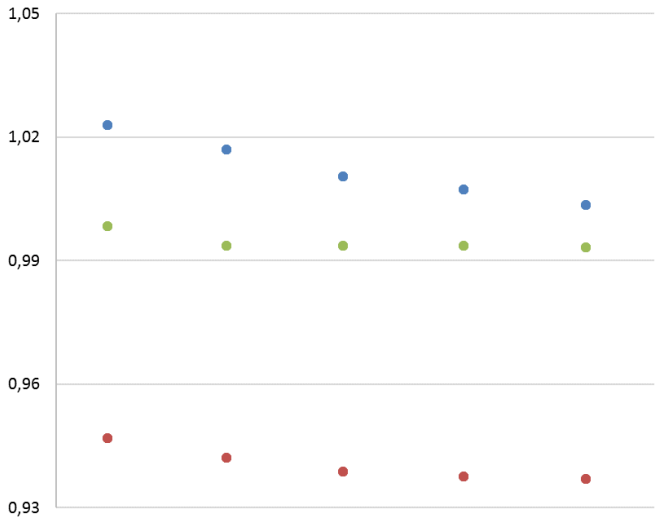


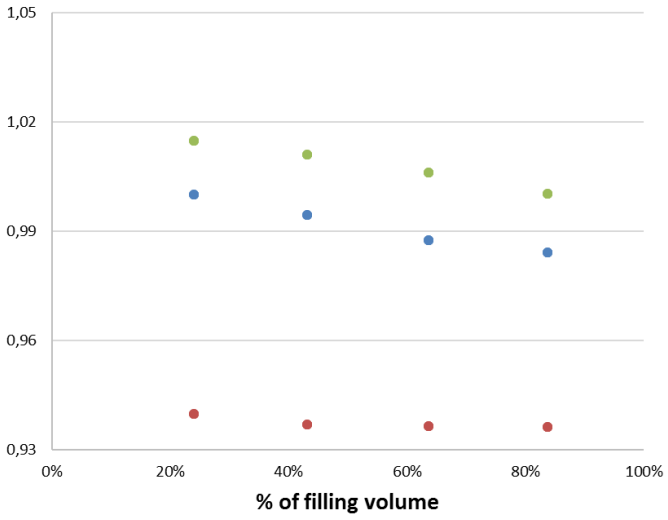
Fig. 40: A_m/A_{true} with respect the percentage of filling volume for a) 5 ml syringe with blue needle b)10 ml syringe with blue needle, filled with ^{18}F



(c)

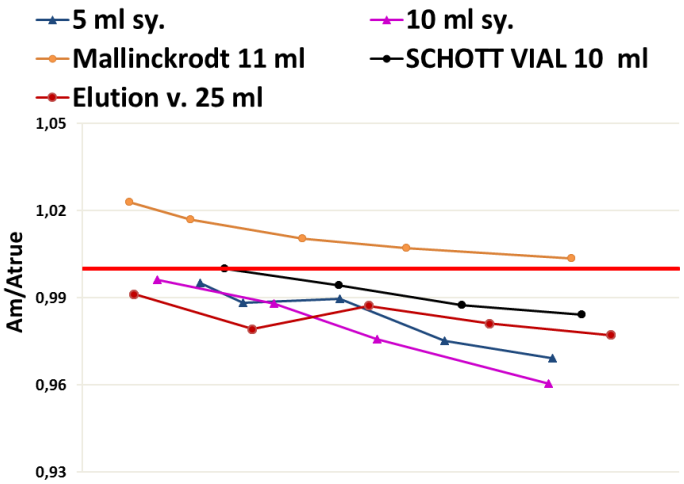


(d)

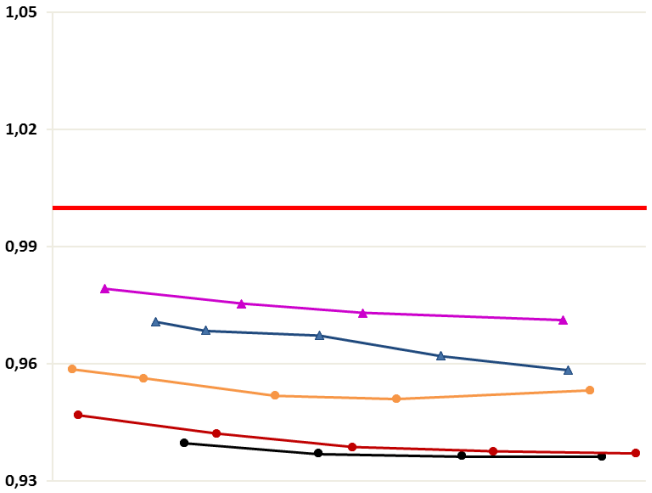


(e)

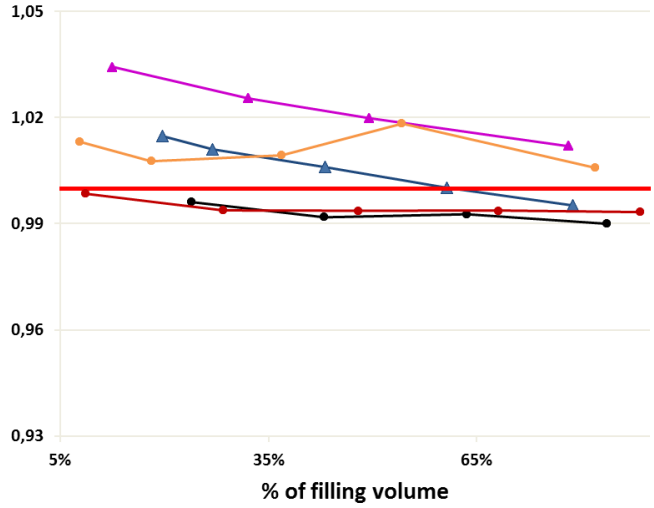
Fig. 41: A_m/A_{true} with respect the percentage of filling volume for c) 11 ml Mallinckrodt, d) TechneVial 25 ml (with A_{true} equal to 385,51 MBq) e) Schott vial 10 ml, filled with ^{18}F.



(a)



(b)



(c)

Fig. 42: A_m/A_{true} with respect the percentage of filling volume for for a) Fidelis, b) Capintec (CRC 55tR) and c) Comecer (VIK 202) RCs, filled with ^{18}F

The values of measured activity for all the RCs show that changes in volume of solution inside the samples produced a negligible difference in activity reading for all the samples: only the 5 ml syringe BN in Fidelis and the 10 ml syringe BD, LL in Fidelis and in VIK 202 produced a difference activity reading equal to the 2%, all the other differences were ≤1% for all the samples in all the RCs.

Capintec CRC-55tR showed a general underestimation for all the samples, and larger in the case of the 25 ml vial for elution (-7%). Mallinckrodt and Schott vials had the same behaviour with a maximum underestimation of about -6%. The measurements in syringes resulted in less overestimation (between -3 and -4% of difference with respect to the nominal value). This RC was the less affected in term of volume in the activity reading.

For Fidelis, measurements in Schott vial 10 ml and Mallinckrodt vial 11 ml were close to the reference value, with only the ±1% of difference for the extreme volumes. All the other samples showed an underestimation which did not exceed 5%.

The measurements in the VIK 202 RCs remained in the range of ±2% of the unitary value for all the samples, but the Mallinckrodt and the Schott vials seemed to be the less affected compared with syringes. For the VIK 203 the result is not shown because only one measurement was performed, which did not allow to draw a conclusion on the behaviour of the RC, even if the ratio between the activity measured and the true activity was in the order of the unitary value.

3.2.5 ^{68}Ga

Figure 43 and 44 show the results obtained with solution of ^{68}Ga, grouped per type of container; while Figure 45 shows the same results grouped by RC. The following are the containers and the reference activity A_{true} of the samples tested: 3 ml syringe BN (130,89MBq), 5 ml syringe BN (228,09 MBq), Mallinckrodt vial 11 ml (597,91 MBq), and Schott vial 10 ml (437,80 MBq). All A_{true} values are specified at the same reference time.

To improve the readability the error bars are not reported in any of the figures. The overall relative uncertainty $u_{\%ratio}$ on the ratio A_m/A_{true} was computed as shown in section 5 of materials and methods (formula (18)). In this case, there were no uncertainties available on the CF for Capintec and Comecer RCs. So, the overall uncertainty for all the RCs was lower than 1% (about 0,34).

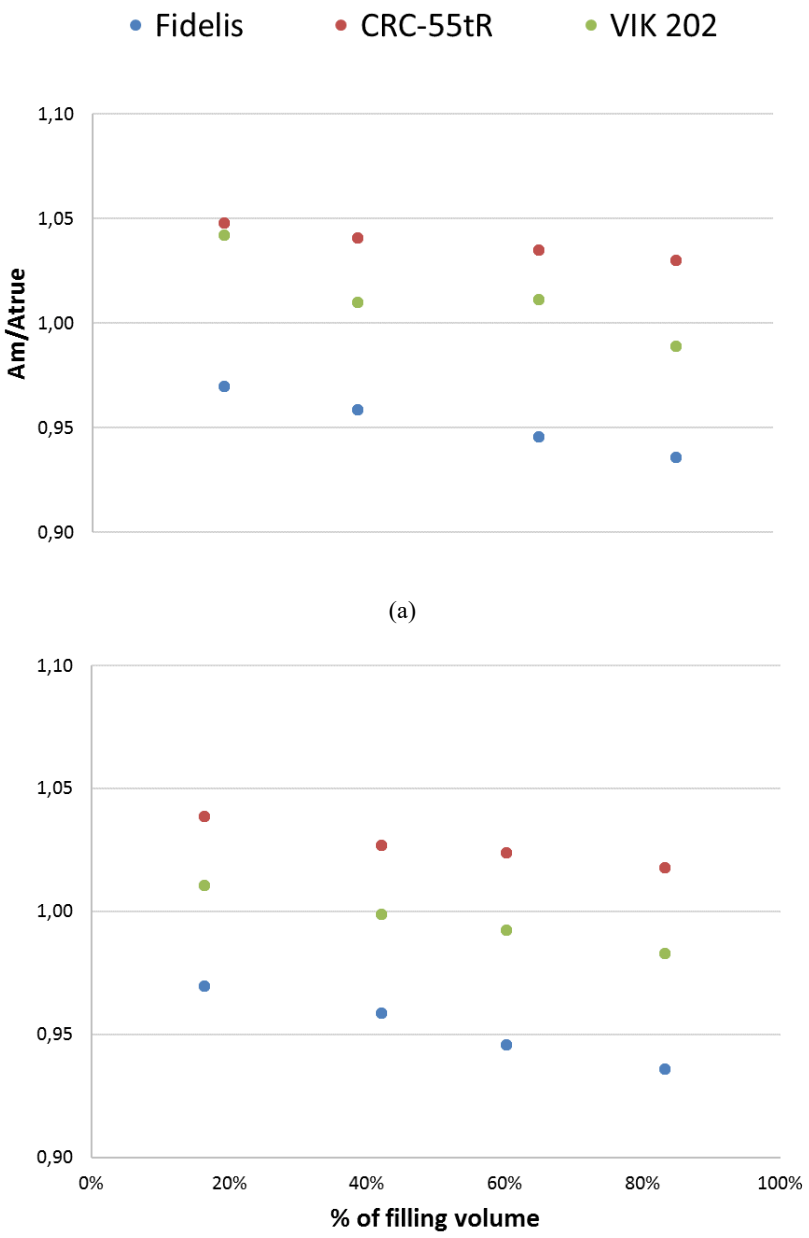
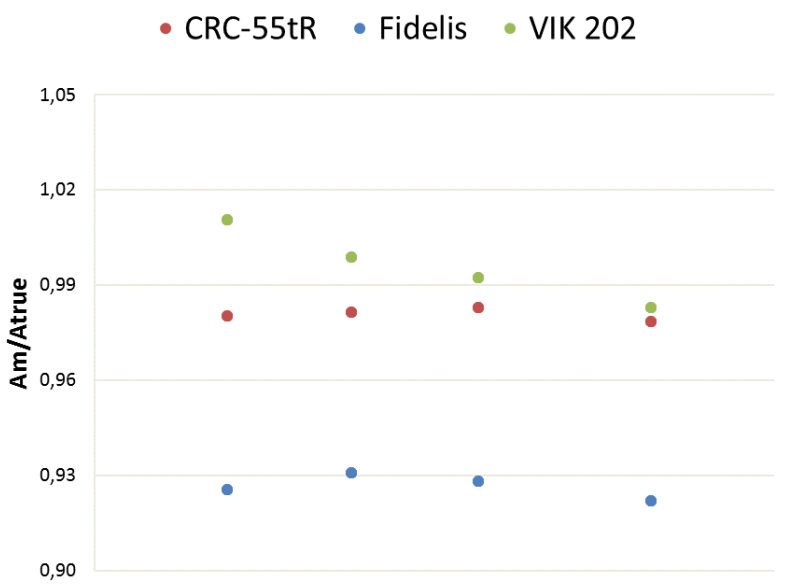
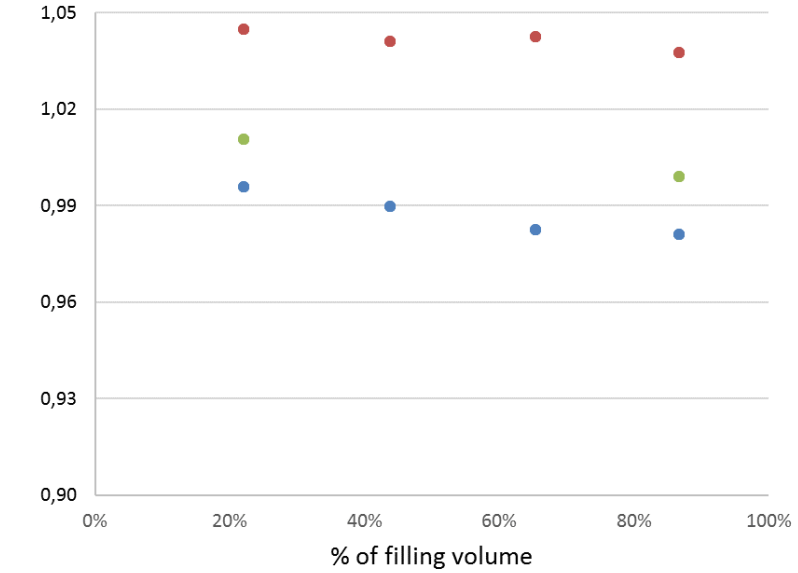


Fig. 43: A_m/A_{true} with respect the percentage of filling volume for for a) 3 ml syringe with blue needle, b)5 ml syringe with blue needle, filled with ^{68}F

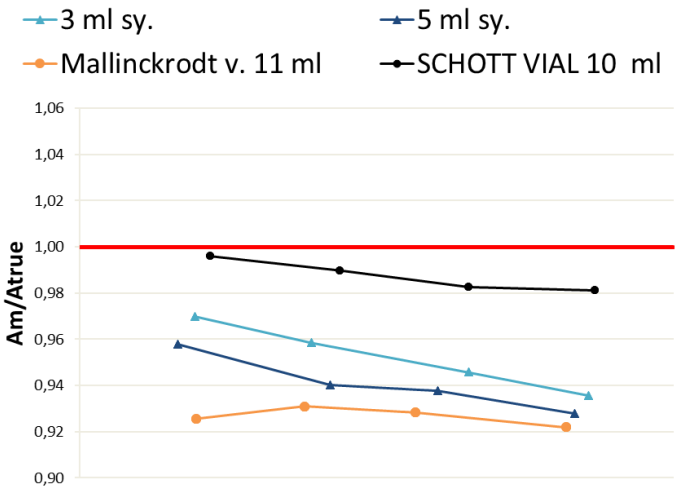


(c)

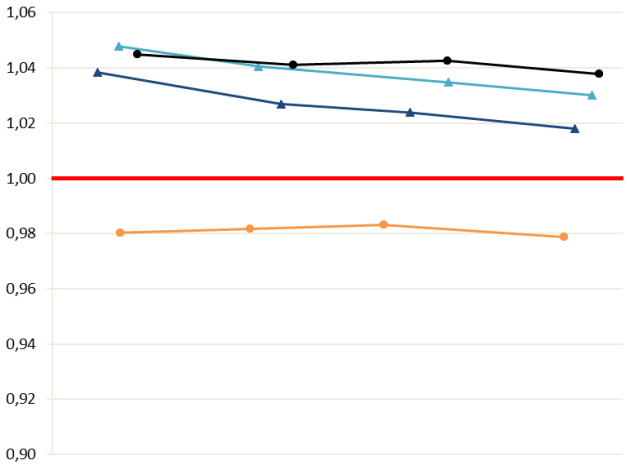


(d)

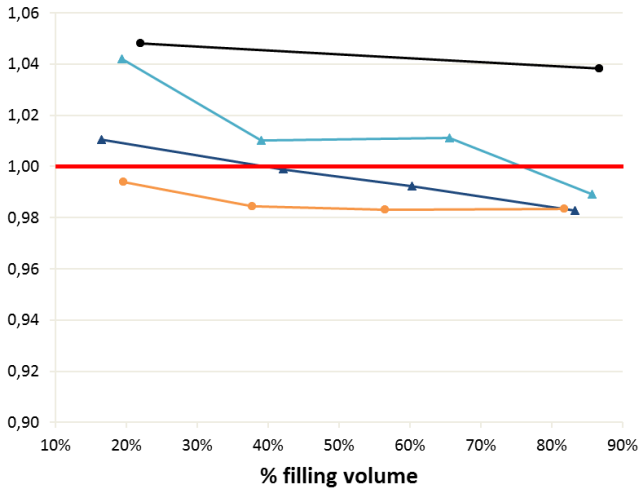
Fig. 44: A_m/A_{true} with respect the percentage of filling volume for c) Mallinckrodt vial 11 ml, d)Schott vial 10 ml, filled with ^{68}Ga



(a)



(b)



(c)

Fig. 45: A_m/A_{true} with respect the percentage of filling volume for a) Fidelis, b) Capintec (CRC 55tR) and c) Comecer (VIK 202) RCs

The values of measured activity for all the RCs showed that changes in volume of solution inside the samples produced a difference in activity reading for all the samples never greater than 5% and only the 3ml syringe BD, LL produced this difference in measured activity in VIK 202 RC. All the other differences were between [1 – 3] % for all the samples in all the RCs.

For ^{68}Ga as for ^{18}F, they are two positron emitters, the geometry dependence affected less the activity measurements compared with the results of low energy radioisotopes. there was a general underestimation of the activity for the 11 ml Mallinckrodt vial for all the RCs, although less accentuated for the VIK 202 RC where the difference with respect to the nominal volume was about 2%.

The measurements in the VIK 202 RC remained in the range of ±5% for all the sample, and the largest difference with respect to the nominal value was given by the Schott vial 10 ml. The 3ml syringe BD, showed a constant behaviour for the intermediate volume measurements, while for the extreme value it showed an overestimation in the case of the smallest volume (+4%) and a small underestimation (-1%) in the case of the largest volume.

Capintec CRC-55tR showed a general overestimation for all the sample except for the Mallinckrodt vial; this measurement, in fact, was underestimated by 2%. The syringes and the Schott vial 10 ml showed the same behaviour, that remain constant also in term of volumes.

For Fidelis, the activity of all the samples were underestimated. The 11 ml Mallinckrodt vial showed the greatest underestimation (7-8%) while the other samples did not exceed (in negative) the value of 5%. In this case, the volume effect for the Fidelis was lower compared with the other radionuclides.

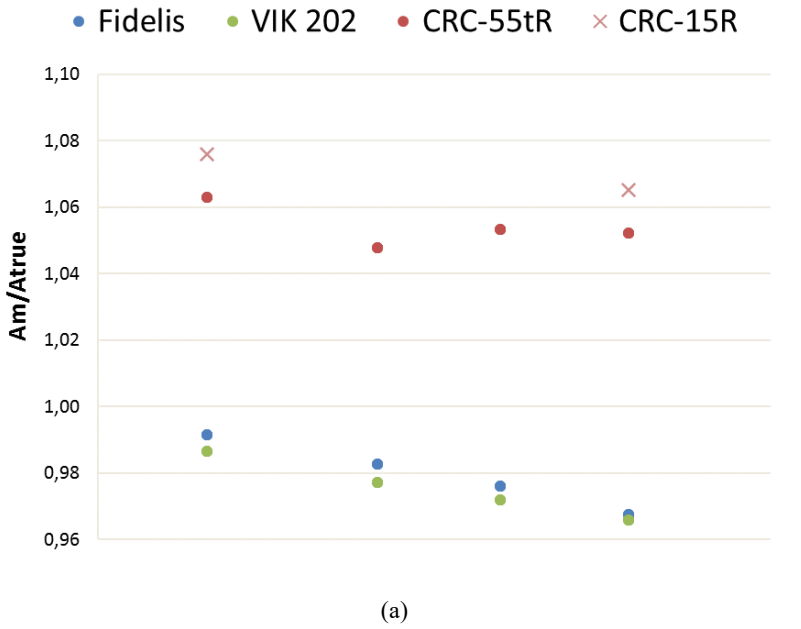
3.2.6 ^{131}I

Figure 46 and 47 show the results obtained with solution of ^{68}Ga, grouped per type of container; while Figure 48 shows the same results grouped by RC. The following are the containers and the reference activity A_{true} of the samples tested: 5 ml syringe BN (39,39 MBq), 5 ml syringe GN (25,41 MBq), Mallinckrodt vial 11 ml (53,97 MBq), elution vial 25 ml (108,53 MBq) and Schott vial 10 ml (84,66 MBq). All A_{true} values are specified at the same reference time.

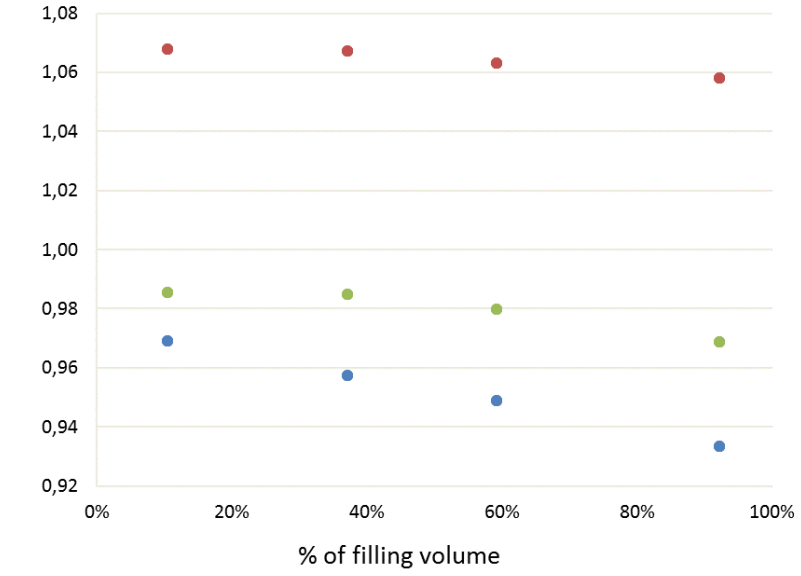
To improve the readability the error bars are not reported in any of the figures. The overall relative uncertainty $u_{\%ratio}$ on the ratio A_m/A_{true} was computed as shown in section 5 of materials and methods (formula (18)):

$$u_{\%\, Am/Atrue} = k\sqrt{u^2_{\%\, A\_true} + u^2_{\%\, A\_m}} \tag{18}$$

For ^{131}I $u_{\%ratio}$ was around 0,4% for Fidelis , around 1.6% (the order of magnitude of uncertainty for CF of Capintec) for Capintenc and around 0,4% for Comecer (in the same order of Fidelis CF uncertainty).

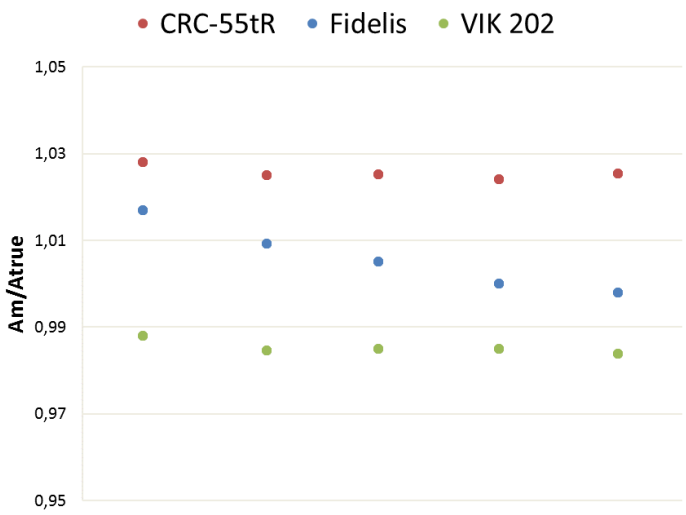


(a)

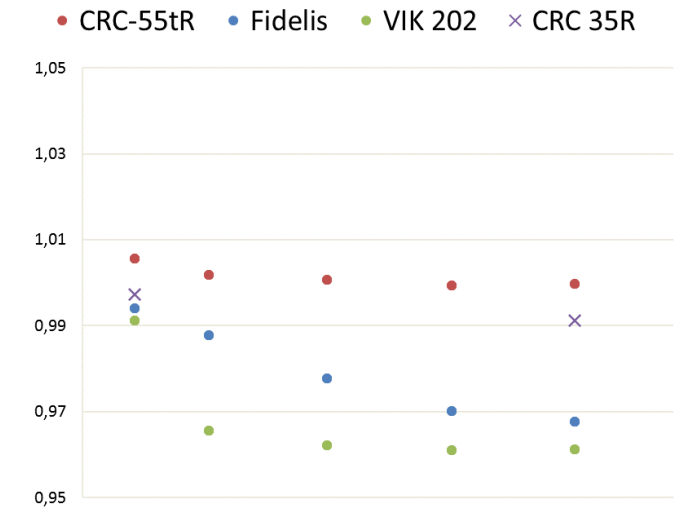


(b)

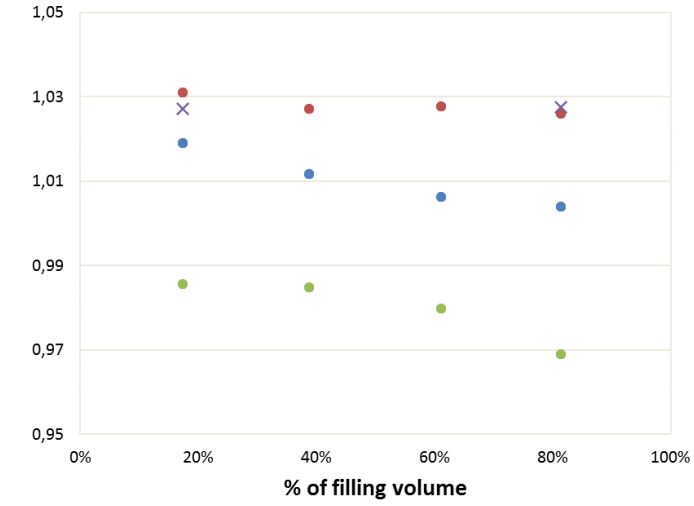
Fig. 46: A_m/A_{true} with respect the percentage of filling volume for a) 5 ml syringe with BN, b) 5 ml syringe with BN measured in Fidelis, VIK 202, Capintec CRC 55tR and CRC 15R, sample filled with ^{131}I



(c)

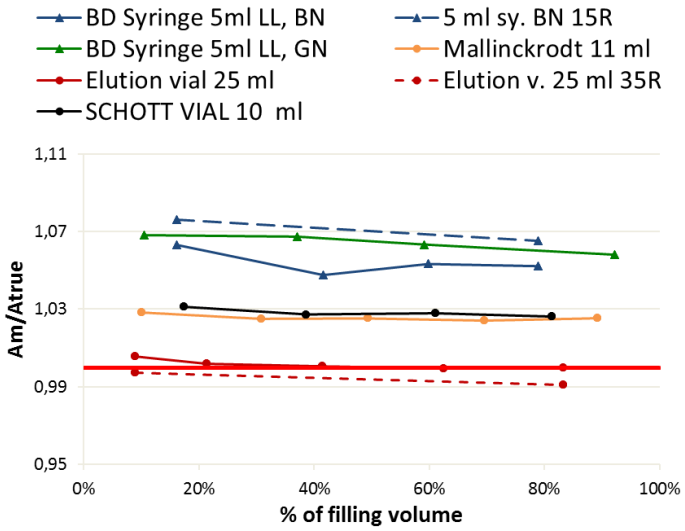


(d)

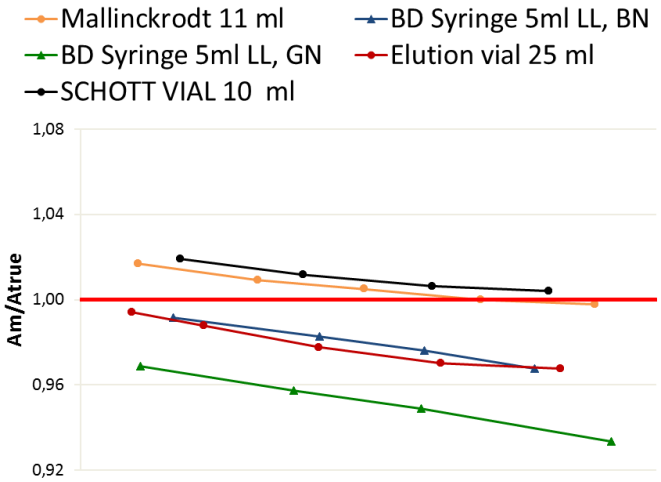


(e)

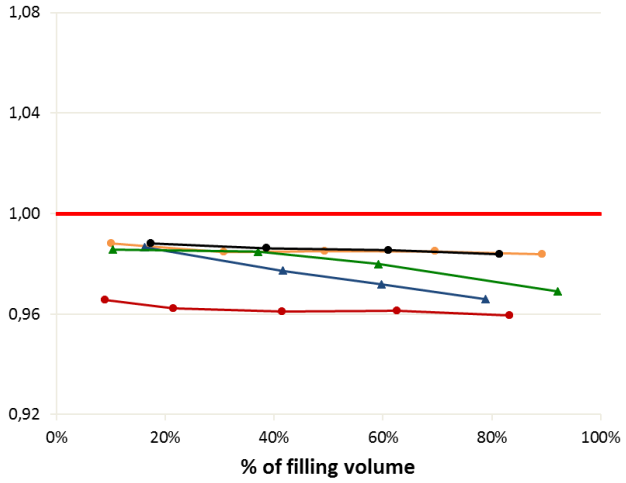
Fig. 47: A_m/A_{true} with respect the percentage of filling volume for c) Mallinckrodt 11 ml vial measured in Fidelis, VIK 202, Capintec CRC 55tR, d) Elution vial 25 ml d) Schott vial 10 ml measured in Fidelis, VIK 202, Capintec CRC 55tR and CRC 35R, sample filled with ^{131}I



(a)



(b)



(c)

Fig. 48: A_m/A_{true} with respect the percentage of filling volume measured in a) Capintec CRC 55tR and CRC 35R b) Fidelis, c) VIK 202, sample filled with ^{131}I

The measurements in the VIK 202 RC showed a general underestimation of the reading activity, however this behaviour was within [0-5] % for all the samples, and the biggest difference with respect to the nominal value was given from the elution vial 25 mm. The two 5 ml syringes show the same behaviour, independently from the presence of the different needle. For the results observed in the case of Capintec RC it is not possible to find an evident explanation.

For all the samples in Fidelis, the measured activity remined in the range of ±6% around unit. Schott and Mallinckrodt vials showed a behaviour more similar to the nominal value with a small overestimation for the smaller volumes (+2%). The other samples showed a smaller overestimation, that for 5 ml syringe is of about the -7%.

The only difference between the 2 syringes of 5 ml BD was the needle. Only Fidelis RC showed an appreciable difference in term of activity reading and, also in this case, this was more likely due to the different position of the sample in the holder.

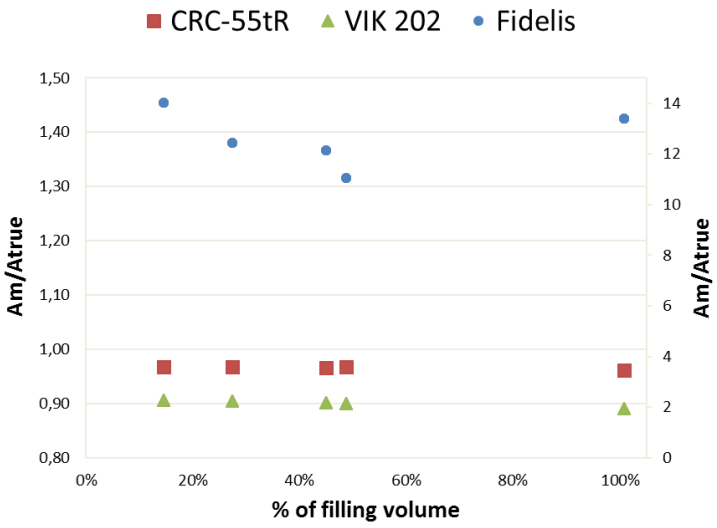
3.2.7 ^{90}Y

Figure 49 and 50 show the results obtained with solution of ^{90}Y, grouped per type of container; while Figure 51 shows the same results grouped by RC. The following are the containers and the reference activity A_{true} of the samples tested: 5 ml syringe BN (1428,07 MBq), KIMAX V-vial 2 ml (280,09MBq) and Schott vial 10 ml (1672,75 MBq). All A_{true} values are specified at the same reference time.

For ^{90}Y there were no uncertainties available on the CF for Capintec and Comecer RCs. So, the overall uncertainty of the ratio A_m/A_{true}, computed as in section 5 (formula (18)):

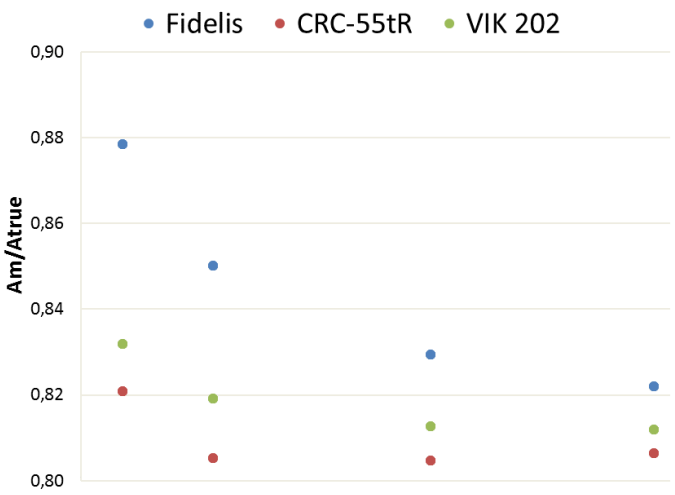
$$u_{\%\ Am/Atrue} = k\sqrt{u^2_{\%\ A\_true} + u^2_{\%\ A\_m}} \tag{18}$$

is in the order of the CF for Schott vial 10 ml in fidelis (0,7%) for all the RCs.

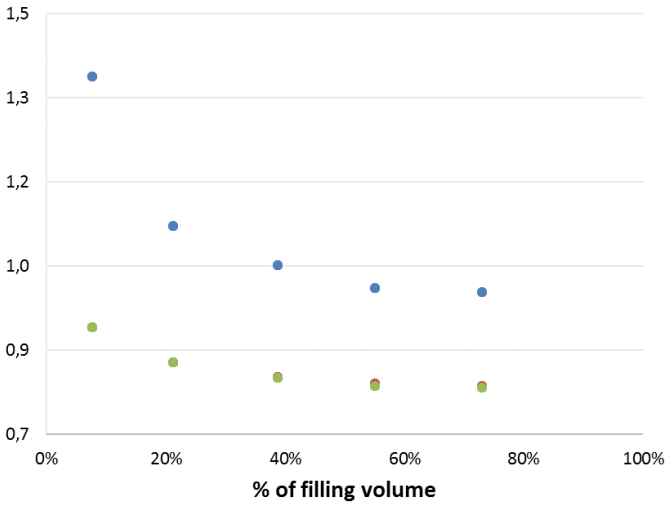


(a)

Fig. 49: A_m/A_{true} with respect the percentage of filling volume measured for a) 5 ml syringe with blue needle. On the left axes are shown the results for Capintec CRC 55tR and Comecer VIK 202 RCs, while on the right axes the result for Fidelis RC

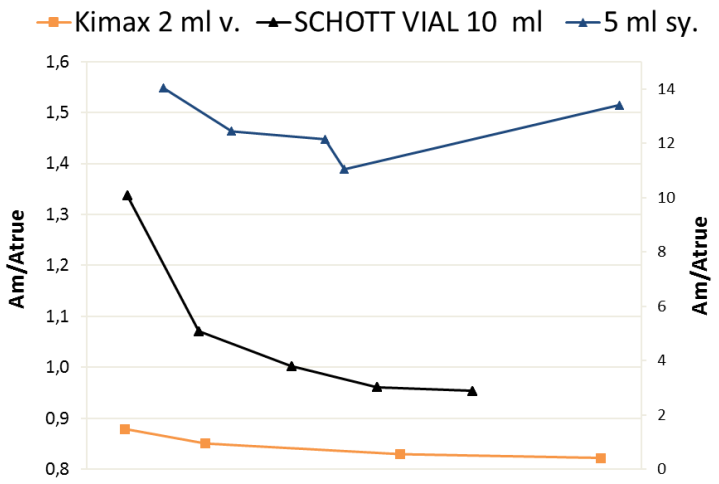


(b)

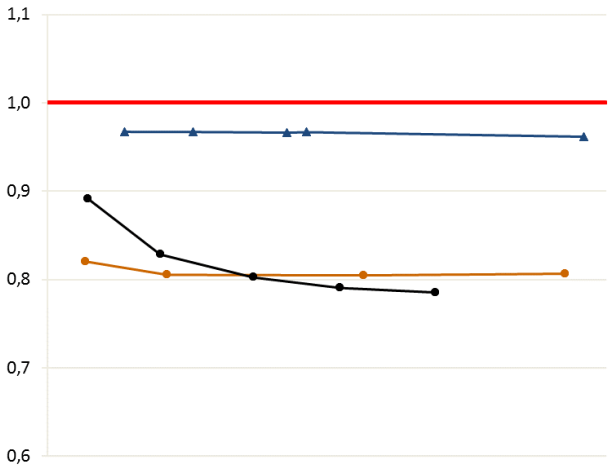


(c)

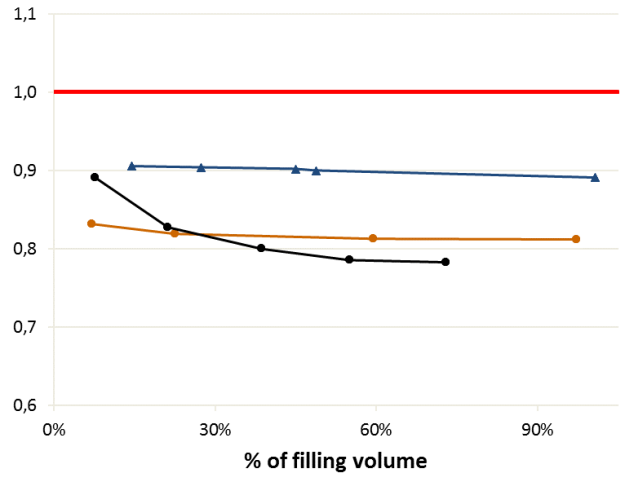
Figura 50: A_m/A_{true} with respect the percentage of filling volume measured for b) KIMAX V-Vial 2 ml and c) Schott vial 10 ml, filled with ^{90}Y



(a)



(b)



(c)

Fig. 51 A_m/A_{true} with respect the percentage of filling volume measured for a) Fidelis (left axis KIMAX V-Vial and Schott vial, right axis 5 ml syringe with blue needle), b) Capintec (CRC 55tR) and c) Comecer (VIK 202), sample filled with ^{90}Y

In the case of Fidelis RC there was an overestimation of the activity measured that was three orders of magnitude greater than the variation/difference observed for the other radionuclides. The ratio between the measured activity and the true one was between 10 and 14 (so A_m was up to 14 times the reference activity A_{true}). This behaviour was a particular of Fidelis only, and might be related to its sensitivity to β- radiation. It seems that the β- particles emitted by ^{90}Y are able to reach the ionisation chamber, increasing the response of the RC.

The glass vials had the same behaviour in all the RCs. The Schott vial 10 ml showed even the same results for measured activity in VIK 202 and for CAPINTEC CRC 55tR. This resulted in an underestimation of the readings that are 20% smaller than the true activity read in the Schott vial 10 ml.

The difference between the volumes were in this case higher than for the other isotopes, in fact, for the Schott these were about 29% for Fidelis, and between 11 and 12% for the other RCs. For the 5 ml syringe in fidelis the amount of difference due to the volume was about 5%.

The penetration power of electrons in a given medium is described by the *stopping power* of the electron. This physical quantity is dependent on the energy of the electron and the properties of the medium (composition, density). The maximum distance that an electron can travel in a medium before it loses all its kinetic energy is described by the physical quantity *range*. An electron of ^{90}Y that is emitted close to the walls of the container will lose some of its kinetic energy when traversing the wall of the container. The amount of kinetic energy lost depends on the material and thickness of the container walls. In Table 15 a rough estimation of the remaining kinetic energy of an electron after it passes through the wall of a glass vial or a plastic syringe is shown. It can be seen that the remaining energy of the electrons is higher for the plastic syringe than for the glass vial, mainly because of the lower stopping power of the plastic (assumed to be polypropylene, PP). Then, in table 16 the electron range in aluminium was calculated for all these remaining kinetic energies, to have an idea of the penetration of electrons in the walls of an ionization chamber (which are usually made of an aluminium alloy).

Table 15: Loss of electron energy due to different container walls. The initial electron energies considered are similar to the average and maximum energy of the beta particles emitted by ^{90}Y of respectively 962 and 2200 keV. The total mass stopping power was assumed to be constant for the energies between the initial electron energy and the calculated remaining electron energy.

Initial electron energy [keV]	Container material	ρ [g/cm3]	wall thickness [cm]	Total mass stopping power [MeV.cm2/g]	Energy lost [keV]	Remaining electron energy [keV]
1000	borosilicate glass	2.23	0.12	1.57	420	580
2000				1.58	424	1576
1000	PP	0.93	0.10	1.94	217	819
2000				1.92	214	1821

Table 16: Penetration of electrons of different remaining energies into the aluminium wall of the ionization chamber.

		Penetration of electrons in the Al walls of the chamber		
Container material	**Remaining electron energy [keV]**	**ρ Aluminium [g/cm3]**	**Mass CSDA range in Al [g/cm2]**	**CSDA range [cm]**
borosilicate glass	550	2.7	0.258	0.10
	1500		0.891	0.33
PP	800		0.421	0.16
	1750		1.058	0.39

Table 16 shows that the range in aluminium of the electrons that passed through the plastic syringe is about 1.6-3.9 mm, depending on the initial energy of the electron; while the range of the electrons passing through the glass vial is lower (1.0-3.3 mm). Considering that the wall of the chamber of RCs is few mm thick (exact thickness not known), some electrons could actually reach the inside of the chamber, in particular for the syringe container. Such electrons would generate a cascade of ionizations in the chamber and result in a much higher ionization current than expected. This could be the reason why measurements of the 5 ml syringe in the Fidelis resulted in a much higher response than measurements of glass vials (both Schott and Kimax vials).

Given that Comecer and Capintec RCs did not show this behaviour (a similar response was observed between the glass vials and the syringe), this suggests that the Fidelis is more sensitive to this type of radiation than the other two RCs. One could hypothesize that this is because the thickness of the chamber wall (and any other material in between the chamber and the sample) is somewhat lower for the Fidelis than for the medical RCs. However, some of the analysis in section 3.2.2 regarding source geometry effects during ^{111}In activity measurements arrived to the opposite hypothesis (that Fidelis might have a slightly thicker chamber and lining walls).

3.2.8 ^{223}Ra

Figure 52 shows the results obtained with solution of ^{223}Ra, grouped per type of container; while Figure 52 shows the same results grouped by RC. The following are the containers and the reference activity A_{true} of the samples tested: 5 ml syringe BN (2,37 MBq), 10 ml syringe with blue needle (3,12 MBq) and Schott vial 10 ml (2,31 MBq). All A_{true} values are specified at the same reference time.

For this radioisotope the uncertainties are given only from the standard deviation on the measurements. For all the devices and all the containers, the overall uncertainty was in the order of repeatability uncertainty (around 0,15%).

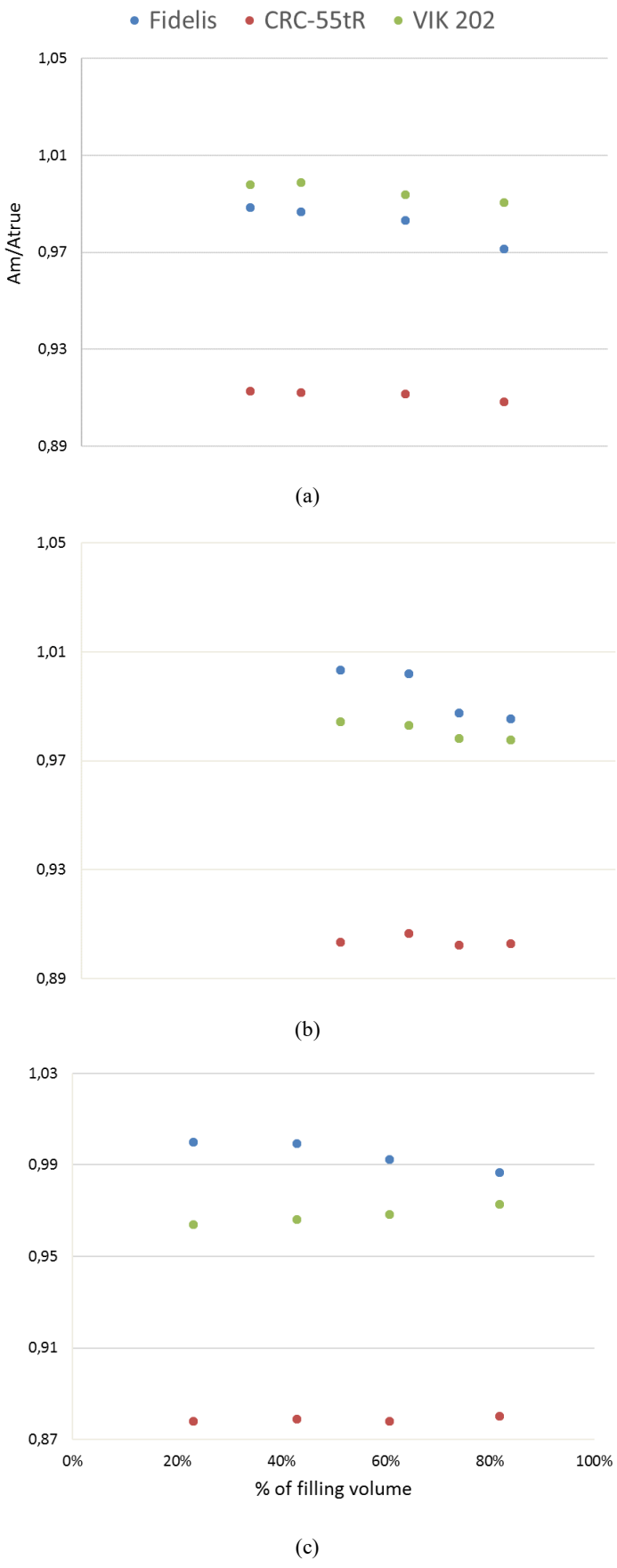


Fig. 52: A_m/A_{true} with respect the percentage of filling volume measured for a) 10 ml syringe with blue needle b) 5 ml syringe with blue needle c) Schott 10 ml vial, filled with ^{223}Ra

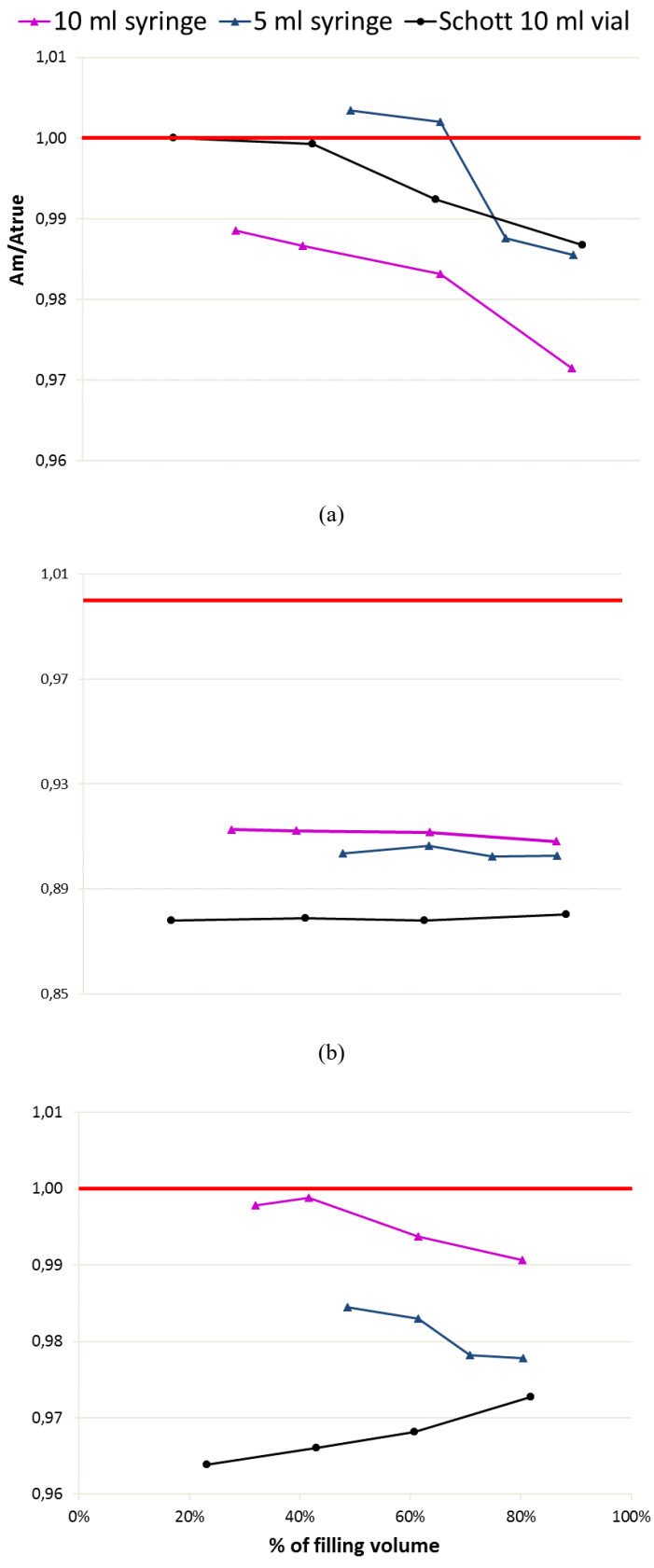


Fig. 53: A_m/A_{true} with respect the percentage of filling volume measured for a) Fidelis, b) Capintec (CRC 55tR) and c) Comecer (VIK 202) RCs

The difference in activity readings between the first and the last volume does not exceed the 2% in any case (for each sample, in each RC).

Capintec CRC 55tR showed an underestimation of the activity of the samples with respect to the other RCs, especially for the 10 ml Schott vial for which the difference between the expected value is about -12%. For the plastic samples, this RC shows an underestimation in the range of the 10%.

Also in the case of VIK 202 it was possible to find a general underestimation of the activity of the sample but, for this RC, the difference with respect to the nominal value did not exceed the 5% (it is more accurate).

Fidelis in this case seemed to be the more accurate in all the activity reading.

4 Accuracy of suppliers' activity

This test was performed on all the samples provided by external manufacturer in their own vials:

- ^{123}I - GE healthcare
- ^{131}I - GE healthcare
- ^{111}In – Mallinckrodt
- ^{223}Ra - Bayer
- ^{90}Y – Ecklert&Ziegler Radiopharma

A table, with all the principal parameters and results, follows below:

Table 17 – Accuracy of the activity stated by the suppliers of different radionuclides.

Radioisotope	$A_{supplier}$ [MBq]	A_{m_supp} [MBq]	$(A_{supplier}/A_{m\_supp} - 1)$ [%]
^{123}I	185	213.12	-13.2%
^{131}I	338.78	334.65	+1.7%
^{111}In	82.72	82.74	-0.02%
^{223}Ra	6.21	5.71	+8.7%
^{90}Y	3700	4586.36	-19%

The accuracy comparisons are taken using the gravimetric method for all the radioisotopes with except for the ^{90}Y, for what it was used the activity method (section 10 in materials and methods).

As it is possible to see all the measurements show an accuracy in the range of ±20%. The most accurate activity received is from Mallinckrodt for the ^{111}In where the difference between the

accuracy measured in Fidelis and the one measured from the manufacturer is only of the 0.02% a value that, considering the uncertainties, is not significant.

The biggest difference is observed for ^{90}Y.

For this radionuclide the reference activity A_{m_supp} was derived using the "activity method" (paragraph 10 materials and methods) because ^{90}Y is absorbed on the walls of the containers, and thus the concentration of ^{90}Y in the solution changes when transferring the solution from one container to another.

CONCLUSIONS

From the preliminary study on the Fidelis RC, carrying out both quality control and characterization tests it appears that the activity measurements are affected by the position of the sample, especially along vertical axes.

Fidelis RC is temperature dependant, and it is necessary a stabilization time of about 30 minutes to use the device in the event that a change in environment conditions is foreseen.

Overall, the good performance of Fidelis RC is confirmed by all the quality control and characterization tests.

In general, from the geometry effect tests performed, it appears that the volume effect influences the activity measurements in a percentage range that is in the order of CF uncertainties for Capintec and Comecer RC while for Fidelis the influence is stronger with respect the computed overall uncertainties (especially for syringes), effect probably due to the fact that the holder does not present a specific hole for the positioning of syringes.

Some verification on the CFs in Comecer and Capintec RCs have to be performed, especially in the case of ^{223}Ra and for the low energy radionuclide emitters (^{111}In and ^{123}I), this is due to the low energy photons emitted by these radioisotopes.

In general, the stronger geometry effect could be notice in the case of the medical vial for ^{99m}Tc (Mallinckrodt 11 ml and the 25 ml vial for the elution of the solution) and in all the plastic syringes in the case of ^{123}I and ^{111}In.

In the first case, the strong underestimation that is possible to notice using the medical vials cannot be noticed for the Schott vial 10 ml, but it can strongly influence the measurements on the activity compromising the correct administration of the radiopharmaceutical to the patient.

The geometry effects for ^{111}In and ^{123}I are due to the presence of a high abundance of low energy photons. This effect is lower in the case of Fidelis and higher in the other two families of RCs, especially in Capintec RCs. It could be mitigate using copper filter. With this kind of holder, however, it is necessary to generate new CFs for the devices. In general, the presence of low energy photons alters the reading in the medical devices and for this reason, besides the application of copper filters and the correction suggested by the manufacturers, it is necessary a recalibration of the devices for avoiding the possibility of incorrect activity measurements.

^{90}Y gives problem in the measurement, especially in Fidelis. So, for this RC it is necessary repeat the test and continue the study for confirming its capability of reading the β-particles; while, for Comecer and Capintec RCs, it is necessary the verification of the CFs used to perform the measurements of the radiopharmaceuticals containing this radioisotope.

In general, the effect of the geometry on the measurements could not considered negligible, even if the values obtained can be considered acceptable for the Hospital measurements. Clearly, it is necessary to take into account this effect and quantify it for a correct administration of radiopharmaceutical to the patient. For this reason, the CFs of RCs available in the hospital must be corrected or directly generated for each specific case, in order to obtain the best possible value of activity reading.

Moreover, even if the accuracy test shows a good performance of all the RCs, there are some exceptions: the low energy emitter ^{123}I and the ^{223}Ra in Capintec RCs. The accuracy of the activity provided by suppliers is lower than currently expected for ^{123}I, for which the value is higher than in all the other cases. For this reason, in the case of direct administration of the radiopharmaceutical using a gravimetric process, it is suggested an activity measurement before delivering it to the patients.

APPENDIX

APPENDIX I – QUESTIONNAIRE DELIVERED TO THE HOSPITALS

QUESTIONNAIRE

Hospital

Name

Your position

Your email

The following questions refer to radionuclides contained in a syringe or in a vial and placed into a RC, for an activity measurement

1. **Can you complete the following table with the values of nominal volume of the container and the value of the volume of solution used for each of these, both for diagnostic and pharmaceutical use?** (If the number of suggested container is not sufficient or If the radionuclides that you use are not present in the list, add them in the empty boxes)

	Vial 1		Vial 2		Syringe 1		Syringe 2		Syringe 3	
	Container size [ml]	**Solution [ml]**	**Container size [ml]**	**Solution [ml]**	**Container size [ml]**	**Solution [ml]**	**Container size [ml]**	**Solution [ml]**	**Container size [ml]**	**Solution [ml]**
I.e. ISOTOPE A					10	7				
Chromium -51										
Fluorine-18										
Gallium-67										
Gallium-68										
Indium-111										
Iodine-123										
Iodine-125										
Iodine-131										
Lutetium – 177										
Radium- 223										
Technetium-99m										
Thallium-201										
Yttrium -90										

Iodine – 131 (pharmaceutical)										
Lutetium-177 (pharmaceutical)										
Radium-223 (pharmaceutical)										
Yttrium-90 (pharmaceutical)										

- VIALS

2. **Which manufacturer do you use for each kind of vial?** (Please write the manufacturer in the first column and in the others the volume of the vials routinely used)

Manufacturer	Volume of the vials in ml				
I.e. MANUFACTURER 1	10	7	//	//	//

3. **Can you decide the manufacturer of vials?**

4. **Are you able to place the vial in the same position of the calibrator during each measurement?**

- SYRINGES

5. **Which kind of syringes do you use?** (Please write the manufacturer in the first column and in the others the material, the volume in ml and the type of tip - if the syringes have a luer lock tip (**LL**) or a luer slip tip (**LS**) - of the syringes routinely used. (See the picture below))

Manufacturer	Material, volume of Syringes in ml and type of tip											
	Material	**Vol.**	**Tip**	**Material**	**Vol.**	**Tip**	**Material**	**Vol.**	**Tip**	**Material**	**Vol.**	**Tip**
I.e. MANUFACTURER1	Glass	10	LL	Plastic	2.5	LS	//	//	//	//	//	//

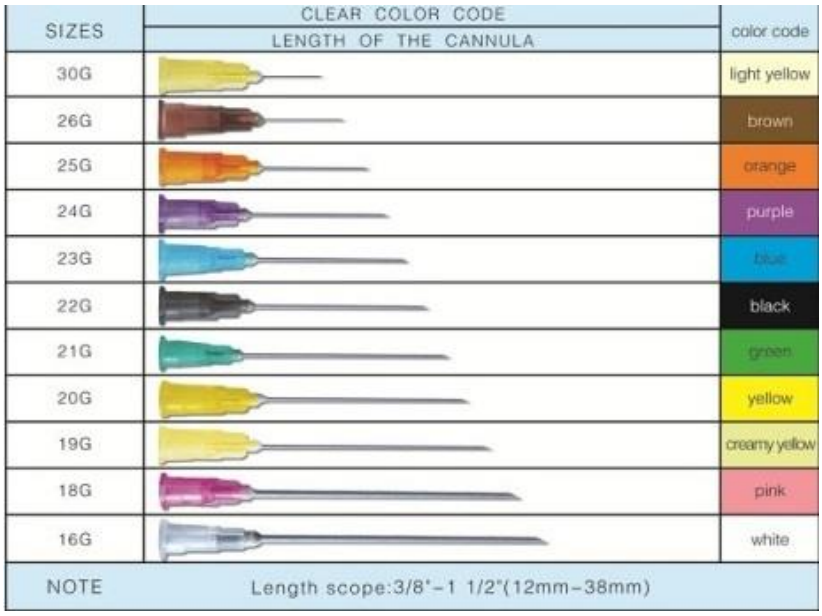
6. **If you use glass syringe, this type of product is used for all the radionuclides or only for a specific one? In the second case, which one?**

7. **In common practice, do you have any control of the type of syringes that you stock?**

8. **Are you able to place the syringe in the same position during each measurement? Do you use a syringe specific holder** (I.e. different design of the holder for different syringes)**?**

9. **Which type of needles do you use routinely?** (Please indicate the manufacturer and the characteristics – **<u>colors, gauge and length</u>**. For more detailed information see the example below the table).

Manufacturer	Type of needle
I.e. MANUFACTURER1	Green, 21 G, 40 mm



10. During the measurement is the needle attached or replaced by a stopper?

11. Any other comments

Many thanks for your co-operation.
Please return this to:
Tel:
Fax:
E-mail:

APPENDIX II – ABSTRACT FROM BOOK OF ABSTRACTS EANM'17, Annual Congress of the European Association of Nuclear Medicine (EANM'17, 2017)

have been performed on 66 consecutive patients (pts) (median age, 62.5 years; age range, 33-91 years) for restaging of newly diagnosed recurrent breast cancer with no previous bone metastases. All pts underwent Spinal MRI of Sagittal T1 and STIR sequences with localized axial T2 imaging along with 18F-NaF PET/CT before initiation of treatment, less than 20 days in between (median: 14 days) in our PET/CT department from September 2010 to March 2016. A nuclear medicine physician with PET/CT experience and a musculoskeletal radiologist evaluated the 18F-NaF PET/CT and MRI studies respectively. Follow-up exams with MRI, CT and 18F-NaF PET/CT as well as CT guided biopsy along with clinical follow up (22pts) (at least 12 months, median time: 19 months) were used as the standard of reference to evaluate 18F-NaF PET/CT and MRI studies. **Results:** On patient-based analysis, 26pts (39.4%) had bone metastases and 40pts (60.6%) was proven bone disease free during follow up. 18F-NaF PET/CT was positive in 40pts (60.6%) showing 97.5% sensitivity, 96.15% specificity, 97.5% positive predictive value (PPV) and 96.15% negative predictive value (NPV). Spinal MRI was positive in 39pts (59.1%) showing 95% sensitivity, 100% specificity, 100% positive predictive value (PPV) and 92.86% negative predictive value (NPV) with disease prevalence of 60.61%. There was concordance of both studies in 63pts (95.5%), MRI was superior in 2 pts (3%) and inferior in one (1.5%) pt. On lesion-based analysis, 18F-NaF PET/CT showed 175 lesions in total, 29 (16.5%) in cervical spine, 71 (40.5%) in thoracic spine, 48 (27.5%) in lumbar spine and 27 (15.5%) in sacrum. MRI revealed 190 lesions in total, 30 (15.8%) in cervical spine, 79 (41.6%) in thoracic spine, 51 (26.8%) in lumbar spine and 30 (15.8%) in sacrum. There was concordance of both studies in 52pts (78.8%), 18F-NaF PET/CT was superior in 4 pts (6%) and inferior in 10 (15.2%) pt on lesion based analysis. **Conclusion:** 18F-NaF PET/CT is a sensitive modality for detection of spine metastases caused by breast cancer. MRI shows a higher specificity but lower sensitivity than 18F-NaF PET/CT, with diagnostic advantage in detecting more spinal metastases, however of uncertain clinical benefit.

E-PW029

Evaluation of the Total Distribution Volume of 18FBPA in Normal Tissues of Healthy Volunteers by Non-Compartmental Kinetic Modeling

***V. Romanov**, K. Isohashi, E. Shimosegawa, T. Watabe, R. Beshr, J. Hatazawa; Osaka University Graduate School of Medicine Department of Nuclear Medicine and Tracer Kinetics, Osaka, JAPAN.*

Background: Boron Neutron Capture Therapy (BNCT) with 4-borono-L-phenylalanine (^{10}BPA) is a promising method of radiation therapy based on ^{10}B(n, α)^{7}Li reaction inside tumor cells loaded with ^{10}B-labeled phenylalanine, causing cell destruction. Very short range of emerged ions (5-9 μm) reduces radiation dose to surrounding normal tissues, however the radiation dose depends on ^{10}B concentration in normal cells. Several studies (by Hanaoka K.; Watabe T.; Shimosegawa E.; Isohasi K.) have been performed in our laboratory to estimate ^{10}B concentration ***in vivo*** using 4-borono-2-[^{18}F]-fluoro-phenylalanine (^{18}FBPA). The purpose of the current study was to evaluate total distribution volume (Vt) of ^{18}FBPA in normal tissues of healthy volunteers by kinetic analysis. **Methods:** 6 healthy volunteers were injected with ^{18}FBPA (3-5 MBq/kg) and 7 PET-CT scans were performed subsequently. ^{18}FBPA radioactivity in whole blood and plasma was measured before, and 8 times after the injection within 50 minutes, using well counter. PET images have been processed by PMOD software (build 3.601). 11 volumetric regions of interest including brain, heart, right lung, spleen, liver, parotid salivary glands, esophagus, stomach, pancreas, intestines, bone marrow were drawn manually for each subject and analyzed with Logan plot (traditional and noise corrected) and Ichise multilinear (MA1 and MA2) models. Better model was defined by Akaike Information Criterion, Schwartz Criterion, Model Selection Criterion, and Coefficient of Determination. Also residual distribution was analyzed visually and using sum of squared residuals and standard deviation of the residuals. An equilibration time t* with maximal allowed error of 1% was set to 20 min for the Ichise MA2 model; to 20 and 28 min for the Ichise MA2 model; to 25 and 33 min for the Logan plot. Finally, Vt values were derived. **Results:** Ichise's MA2 model showed best fitting among all models. Vt values ranged from 0.94±0.14 ml/ccm in the pancreas to 0.15±0.01ml/ccm in the lung. **Conclusion:** Maximal Vt value of ^{18}FBPA did not exceed 1.09 ml/ccm, being much lower than values published for tumors as Vt itself (Grunewald C. et al., 2016) or those that could be derived from rate constants (J.C Chen et al. 2004; Imahori Y. et al., 1998), thereby reflecting lower K1/k2 ratio in normal tissues. Vt values obtained in this study could potentially be used for evaluation of ^{10}B concentration in normal tissues before BNCT with ^{10}BPA constant infusion protocol, however comparison of the estimated results with real boron concentration in normal tissues is needed.

E-PW04 **Monday, October 23, 2017, 08:30 - 09:30, e-Poster Walk Area, Level 2, Foyer A, Screen 1**

Do.MoRe: SPECT Technology

E-PW030

Uncertainty in activity measurements using radionuclide calibrators due to source geometry effects

***C. Saldarriaga Vargas**[1], A. Carbutti[2], J. Dabin[1], K. Baete[3], L. Struelens[1]; [1]Belgian Nuclear Research Centre (SCK-CEN), Mol, BELGIUM, [2]Politecnico di Torino, Turin, ITALY, [3]UZ Gasthuisberg, Leuven, BELGIUM.*

This study aimed to evaluate the uncertainty in activity measurements of clinical radioisotopes due to source geometry effects for different radionuclide calibrators (RC). Experiments were performed to assess the effect of container type and solution volume on the measurement accuracy. ^{18}F, ^{68}Ga, ^{99m}Tc, ^{111}In, ^{123}I, ^{131}I, ^{90}Y (chloride form) and ^{223}Ra were studied in various clinical containers, including 1-10ml plastic syringes and 2-25ml glass vials. A stock solution (SS) of each radionuclide was prepared in a standard 10ml Schott vial, and the reference activity concentrations were determined using a Fidelis Secondary Standard

RC. SS was then transferred to each container, and its reference activity was determined from the mass of the transferred solution and the SS activity concentration. The solution inside each sample was diluted with water to test for volume effects. Radioactivity was measured after preparation and following each dilution, both in the Fidelis and in RCs from Capintec and Comecer. Results showed that the activity read by all RCs is dependent on the container type. The RC response is usually higher (up to 40%) when the activity is measured in a syringe rather than in a clinical vial. This effect is stronger for radionuclides emitting low-energy photons: for ^{123}I and ^{111}In, field instruments can overestimate the activity in a syringe by 15-28%, whereas in a glass vial the activity can be underestimated by 5-15%. ^{18}F and ^{131}I were the radionuclides the least affected by the container type; however, measurements were not necessarily within ±5% of the reference value. In general, measurements were more accurate in the Schott vial than in clinical containers, probably because this container is more similar to the containers used by the manufacturers to calibrate the RCs (***e.g.*** thin-walled glass ampoules). Regarding volume effects, the difference in activity reading between filling volumes, corresponding to about 20% and 80% of the nominal container size, was usually negligible or within 3-5% for most samples and RCs tested. Activity measurements using RCs can be strongly affected by the sample container. It is recommended to quantify these effects during acceptance/performance testing of RCs using the radiopharmaceuticals and containers most frequently used in clinical practice. If necessary, container-specific calibration (or correction) factors can be determined to improve the accuracy of radioactivity measurements in routine nuclear medicine. Finally, the accuracy of the activity reported by the suppliers of some radionuclides was also evaluated and is currently being analyzed.

E-PW031

Accuracy, Repeatability and Reproducibility of xSPECT Quant Sensitivity Calibrations using a NIST-traceable Point Source

*P. C. Holdgaard[1], H. C. Larsen[1], **N. A. Bebbington**[2]; [1]Lillebælt Hospital, Vejle, DENMARK, [2]Siemens Healthineers, Aarhus, DENMARK.*

Introduction: Before clinically interpreting quantitative values it is important to understand the error on the final measurement. A potential source of error in absolute SPECT quantification is the scanner sensitivity calibration. Sensitivity calibrations should be accurate, repeatable, reproducible, and should be representative of sensitivity across the detector. The aim was to assess accuracy, repeatability and reproducibility (over time and spatially across the detector) of sensitivity calibrations made according to the Siemens xSPECT Quant method using a NIST traceable Co-57 source. **Subjects and Methods:** Reproducibility with time: 35 sensitivity calibrations were made using a NIST-traceable Co-57 point source across two Siemens Symbia Intevo 6 systems (software version VB10), according to standard protocol, over a one-month period. Reproducibility across the detector: 11 sensitivity measurements were made across a 10cm distance in the z-direction in 1cm increments on one system. Repeatability: 15 sensitivity calibrations were made in succession (with and without moving the source between measurements) on one system. Accuracy: a uniformity phantom filled with 51.3MBq Tc-99m-TcO_4^- (as measured on a Capintec CRC15 dose calibrator) was scanned, and reconstructed with the quantitative OSCG algorithm, and the measured SUV compared to the known SUV of 1.00. **Results:** Accuracy: using a factor to correct for dose calibrator bias from prior cross-calibration between scanner and dose calibrator (as information on traceability of the dose calibrator to a primary standard was not available), the SUV of the Tc-99m uniformity phantom measured 1.00. Reproducibility with time: mean (±SD) sensitivity calibration factors (SCF) for detectors 1 and 2 were 88.5(±0.3%)cps/MBq and 88.0(±0.2%)cps/MBq for scanner 1, and 87.6(±0.2%)cps/MBq and 88.1(±0.3%)cps/MBq for scanner 2. Spatial reproducibility of SCF across the detector: Mean (±SD) SCF was 87.7(±0.4%)cps/MBq and 88.1(±0.5%)cps/MBq for detectors 1 and 2 respectively. Repeatability: without moving the source between measurements, standard deviations were 0.0% and 0.1% for detectors 1 and 2. When the source was moved between measurements, standard deviations were 0.1% and 0.2%. **Conclusions:** These findings demonstrate that xSPECT Quant sensitivity calibrations made using a NIST-traceable Co-57 point source give excellent accuracy, repeatability, and reproducibility with time and with location across the detectors. This method of sensitivity calibration thus contributes only an extremely small error to the final quantitative SPECT measurement, which is much less than is expected with manual Tc-99m calibration methods.

E-PW032

Determining the calibration factor of a SPECT/CT camera

L. Beels[1], F. Lavent[1], I. Decostere[2], L. Tack[2], C. Van de Wiele[1], A. Maes[1]; [1]AZ Groeninge, Kortrijk, BELGIUM, [2]KU Leuven, Leuven, BELGIUM.

Aim: Quantitative single-photon emission computed tomography (SPECT) has several important applications including monitoring tumor response after treatment and dose estimation for targeted radionuclide therapy treatment planning. The use of a calibration factor is required to obtain quantitative SPECT images. In this study, the calibration factor (CF) was determined for different acquisition and reconstruction protocols. **Materials and Methods:** A cylindrical phantom (height: 19.5 cm , diameter: 19.5 cm) was used for the SPECT/CT acquisitions (GE Discovery NM/CT 670). The phantom was filled with ^{99m}Tc, approximately 320 MBq for the first measurements and approximately 230 MBq for the second measurement that was performed to check the reproducibility of the calibration factor. The phantom was acquired four times using different acquisition parameters (change of acquisition time, matrix size, zoom factor) and the phantom was reconstructed using the GE Xeleris Volumetrix and GE Xeleris Volumetrix Evolution for Bone software. A volume of interest (VOI) (height: 15 cm, diameter: 17 cm) was drawn on the acquired images. Knowing the counts in the VOI, the volume of the VOI and the acquisition time, the count rate per unit volume was calculated. The CF was then determined by dividing the count rate per unit volume by the activity con-

APPENDIX III – E-Poster from EANM'17 CONFERENCE

Uncertainty in activity measurements using radionuclide calibrators due to source geometry effects

C. Saldarriaga Vargas[1], A. Carbutti[2], J. Dabin[1], K. Baete[3], L. Struelens[1]

[1] Belgian Nuclear Research Centre (SCK•CEN), Mol, Belgium; [2] Politecnico di Torino, Turin, Italy; [3] UZ Gasthuisberg, Leuven, Belgium

csvargas@sckcen.be

Introduction

- In nuclear medicine **radionuclide calibrators (RC) are used to quantify radiopharmaceutical activity** prior to patient administration. Moreover, they can be used as a **reference instrument to cross-calibrate other devices** like gamma cameras and gamma counters.
- In **clinical practice** RC measurements are performed in a **variety of clinical containers** which differ in size, shape and wall thickness; and that are **different** from the standard **containers used at calibration**. This can lead to **significant errors in the radioactivity assay** of clinical radionuclides.
- With the **growing need of quantitative accuracy in nuclear medicine,** a more detailed knowledge on the **uncertainties associated to clinical activity measurements** using RCs becomes **necessary.**

Objective

This study aimed to **evaluate the uncertainty in activity measurements** of clinical radioisotopes **due to source geometry effects** for different RCs.

Materials and Methods

The **effect of container type and solution volume on the accuracy of RC measurements** was assessed for the following radionuclide solutions:

Table 1. Clinical radionuclide solutions tested.

Radionuclide	Supplier	Active form	Half-life	$E_{\gamma/X\text{-ray}}$ [keV] (emission prob. %)
^{18}F	Cyclotron UZ Leuven, BE	Na fluoride (^{18}F)	110 m	511 (194%)
^{68}Ga	^{68}Ge/^{68}Ga generator	^{68}Ga-chloride	68 m	1077 (3%), 511 (178%)
^{90}Y	Sirtex Medical (distrib. Eckert & Ziegler Radiopharma, GE)	^{90}Y-trichloride	2.7 d	-
^{99m}Tc	^{99}Mo/^{99m}Tc generator	Na pertechnetate (^{99m}Tc)	6.0 h	141 (89%), 18-21 (8%)
^{111}In	Mallinckrodt Medical, NL	^{111}In-oxine	2.8 d	245 (94%), 171 (91%), **27 (15%), 23 (68%)**
^{123}I	GE Healthcare, NL	Na iodide (^{123}I)	13.2 h	159 (83%), **31-32 (16%), 27 (71%)**
^{131}I	GE Healthcare Buchler, GE	Na iodide (^{131}I)	8.0 d	637 (7%), 364 (81%), 284 (6%), 29-34 (5%)
^{223}Ra	Bayer (distrib. IFE, NO)	^{223}Ra-dichloride	11.4 d	338 (3%), 324 (4%), 269 (14%), 154 (6%), 94-98 (11%), 81-84 (39%), 10-17 (22%)

A stock solution (SS) of each radionuclide was prepared in a standard 10 ml Schott Type 1+ vial, and its **reference activity concentration was determined using a Fidelis Secondary Standard RC** (Southern Scientific Ltd, UK).

Samples were prepared from the SS in a variety of containers (Fig. 1). The **reference activity A_{ref}** of each sample was determined from the SS activity concentration and the mass of transferred SS.

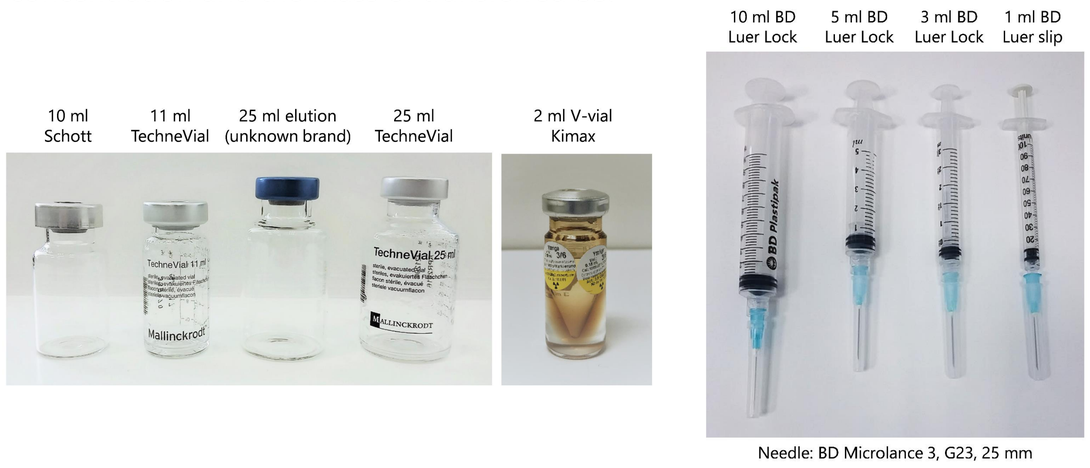


Figure 1. Containers used to prepare the samples.

The solution inside each sample was diluted with water to test for volume effects.

Sample activity was measured (A_m) after preparation and following each dilution, both in the Fidelis and in two field RCs: **CRC-55tR** (Capintec Inc, USA) and **VIK-202** (Comecer Netherlands, NL).

Table 2. Radionuclide calibration factors (CF) used.

	Fidelis			
	CF Fidelis [pA/MBq]	$u_{CF\ Fidelis}$ [%]	CF CRC 55tR	CF VIK 202
^{18}F	10.39	1.10%	472	762
^{68}Ga	10.32(§)	0.34%	416	749
^{90}Y	0.0721	0.70%	48 x 10	902(v), 890(s)
^{99m}Tc	1.24	0.90%	080	236
^{111}In	4.129	0.75%	303	711(v), 696(s)
^{123}I	1.721	0.90%	277	618
^{131}I	4.073	0.40%	151	480
^{223}Ra	3.166	0.38%	268(*)	(*)

(§): CF for P6 vial instead of schott vial.
(v): CF for vial containers.
(s): CF for syringe containers.
(*): CF determined by hospital using a standard from radionuclide supplier.

Solutions were assumed to be free of radionuclide impurities.

No corrections for volume or container effects were applied to A_m.

The standard **uncertainty on A_{ref} was below 1.2%** for all radionuclides, and accounts only for the uncertainty of the Fidelis CFs for a Schott vial (Table 2).

Results

Container effects:

Table 3. Ratio between A_m and A_{ref} for samples prepared using different containers filled at about 40% of their nominal capacity.

% overestimation: + (15->35)% | + (5-15)% | ± [0-5]% | % underestimation: - [15-5)% | - [35-15)%

A_m / A_{ref}		BD plastic syringe 1 ml	3 ml	5 ml	10 ml	Glass vials Schott 10 ml	Mallinckrodt 11 ml	Elution 25 ml (*)	V-vial 2 ml
^{18}F	Fidelis			0.99	0.99	0.99	1.01	0.99	
	CRC-55tR			0.97	0.98	0.94	0.95	0.94	
	VIK-202			1.01	1.03	0.99	1.01	0.99	
^{68}Ga	Fidelis		0.96	0.94		0.99	0.93		
	CRC-55tR		1.04	1.03		1.04	0.98		
	VIK-202		1.01	1.00			0.98		
^{90}Y	Fidelis			12.15		1.00			0.85
	CRC-55tR			0.97		0.80			0.81
	VIK-202			0.90		0.80			0.82
^{99m}Tc	Fidelis	0.90	0.89	0.98		1.00	0.79	0.79	
	CRC-55tR	0.90	0.90			0.99	0.78	0.79	
	VIK-202	0.91	0.90	0.99		1.01	0.80	0.81	
^{111}In	Fidelis		1.00	0.99		0.99	0.98		
	CRC-55tR		1.29	1.25		1.03	1.01		
	VIK-202		1.02	0.99		0.89	0.87		
^{123}I	Fidelis		1.03	1.02		1.00	0.97		
	CRC-55tR		1.30	1.26		0.96	0.93		
	VIK-202		1.17	1.14		0.92	0.89		
^{131}I	Fidelis			0.98		1.01	1.01	0.98	
	CRC-55tR			1.05		1.03	1.03	1.00	
	VIK-202			0.98		0.99	0.98	0.96	
^{223}Ra	Fidelis			1.00	0.99	1.00			
	CRC-55tR			0.90	0.91	0.88			
	VIK-202			0.98	1.00	0.97			

(*): Vial brand: Mallinckrodt TechneVial for ^{18}F, GE Healthcare for ^{99m}Tc, generic (unknown brand) vial for ^{131}I.

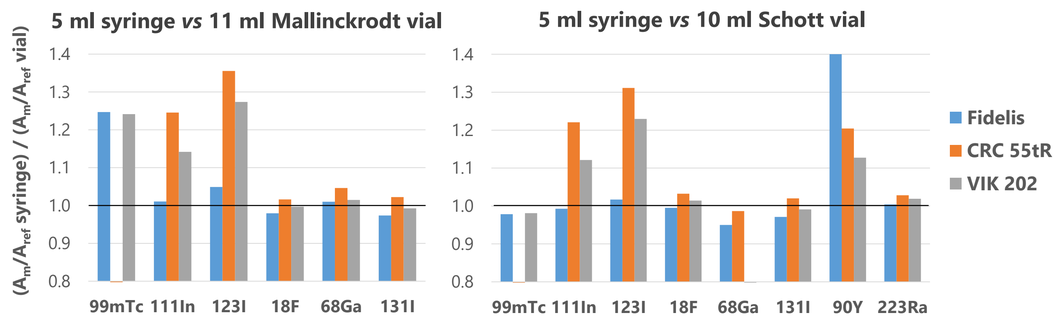


Figure 3. RC response using a 5 ml plastic syringe vs the response using a glass vial.

Volume effects:

A_m is 3-5% lower when the volume of solution is increased from ~20% to 70-90% of the nominal capacity of the container.

Discussion

^{131}I, ^{18}F, ^{68}Ga and ^{223}Ra:

- The **container dependence is < 5%.**
- Most RC measurements are **accurate within ±5%.**

^{123}I, ^{111}In, ^{99m}Tc and ^{90}Y:

- RC measurements are **largely affected by the container type**. **Syringe samples result in an increased RC response** compared to (clinical) glass vials (Fig. 3). This always has a **negative impact on the measurement accuracy** of at least one type of container.
- There is a **tendency to underestimate the activity in clinical glass vials**. ^{99m}Tc and ^{90}Y are the radionuclides most affected (**20% underestimation**).
- Instead, the **activity in a syringe can be overestimated up to 30%** (^{123}I and ^{111}In); and results of ^{99m}Tc, ^{111}In and ^{123}I indicate that the measurement error is higher for smaller (1 or 3 ml) syringes.
- Manufacturer corrective factors for container effects (*e.g.* ±10% for ^{111}In, ±15% for ^{123}I) do not always fully compensate the measurement error (±25%).

Fidelis SSRC:

- This RC is less dependent on container type than field RCs. A_m is usually accurate within ±3%. Indeed the Fidelis is a Secondary Standard RC.
- ^{90}Y activity in a syringe is largely overestimated. This is likely to be due to ^{90}Y energetic betas reaching the sensitive region of the chamber.

Conclusion

- The **effect of container on RC measurements should not be neglected.** Container **correction factors up/down to ±25% are required** to accurately quantify the activity of **^{123}I, ^{111}In, ^{99m}Tc and ^{90}Y** in some clinical containers.
- **Filling volume has a smaller effect (<5%)** on the RC assay.
- Hospitals are encouraged to follow an **experimental verification of the accuracy of their RCs by means of traceable standards of activity** for the radionuclides and source geometries relevant in clinical practice. Such measures are recommended to comply with the **growing need for quantitative accuracy in nuclear medicine**.

List of Figures

List of Tables

Bibliography

(CPEP), Contemporary Physics Education Project. (2003). *Nuclear Science - A guide to the Nuclear Science Wall Chart.*

Aerts A., I. N. (2014). Biologican carrier molecules of radiopharmaceuticals for molecular cancer imaging and targeted cancer therapy. *Current pharmaceutical design*, 5218-44.

Baker, M. (2005). Calibration of the NPL secondary standard radionuclide calibrator for the new 10R Schott, Type 1+ vials. *Applied Radiation and Isotopes 63*, 71-77.

Capintec, I. (1995). *CRC 35R - Radioisotope Dose Calibrator - Owner's Manual.* Ramsey: Capintec, Inc. .

Capintec, I. (2007). *CRC-15R - Radioisotope Dose Calibrator - Owner's Manual.* Ramsey, New Jersey : Capintec, Inc. .

Capintec, I. (2010). *CRC - 55t - Owner's Manual.* Ramsey, New Jersey: Capintec, Inc.

D. L. Baily, J. H.-P. (2014). *Nuclear Medicine Physics; A handbook for teachers and students.* Vienna: IAEA.

D.L. Bailey, J. H.-P. (2014). *Nuclear Medicine Physics - A Handbook for Teachers and Students.* Vienna: IAEA .

EANM'17. (2017). European Journal of Nuclear Medicine and Molecular Imaging. *Annual Congress of the European Association of Nuclear Medicine* , *44*, pp. 238-239. Vienna, Austria .

Environmental Health and Safety - Washington University. (2006). Principles of radiation protection. In *Principles of radiation protection.* Washington.

Gabriel Candelaria, D. I. (2010). *The Science of Measurement: a primer on Radioactivity Dose Calibrators.* New Mexico.

Gabriel, C., & Irwin, D. (2010). *The Science of Measurement: A Primer on Radioactivity Dose Calibrators.* University of New Mexico Health Science Center. Christina Muñoz.

GTCCEIS. (n.d.). Retrieved from Greater-Than-Class C Low-Level Radioactive Waste EIS Information Center web site: (http://gtcceis.anl.gov/images/photos/PenetratingRad.gif)

IAEA. (1991). *Quality Control of Nuclear Medicine Instruments.* Vienna: IAEA.

IAEA. (n.d.). *IAEA*. Retrieved from https://humanhealth.iaea.org/HHW/Radiopharmacy/VirRad/Quality_Control_Procedures/Quality_Control_Module/Radioactivity_concentration/Measurement_tools/Isotope_Calibrator/Principles_of_an_isotope_calibrator/index.html

Integrated Publishing, I. (n.d.). *Integrated Publishing, Inc.* Retrieved from Integrated Publishing, Inc. web site: http://nuclearpowertraining.tpub.com/h1013v2/css/Geiger-Mller-Detector-66.htm

Kallini J. R., G. A. (2016). Thansarterial Radioembolization with Yttrium-90 for the Treatment of Hepatocellular Carcinoma. *Advances in Therapy*, 699-714.

Knoll, G. F. (n.d.). *Radiation detection and Measurement.* Michigan : Jhon Wiley and Sons, Inc. .

Kowalsky, R. J., Johnston, E. R., & Chan, F. H. (1977). Dose Calibrator Performance and Quality Control. *Journalof NUCLEAR MEDICINE TECHNOLOGY*, 35-40.

LNHB. (2017, march 3). *Laboratoire National Henri Becquerel Recommended data*. Retrieved from Laboratoire National Henri Becquerel: http://www.nucleide.org/DDEP_WG/DDEPdata.htm

Loveland, W., Morrisey, D. J., & T, S. G. (2006). *Modern Nuclear Chemistry.* Hoboken, New Jersey : John Wiley & Sons, Inc.

M., B. (2005). Calibration of the NPL secondary standard radionuclide calibrator for the new 10R Schott, type 1+ vials. *Applied Radiation and Isotopes*, 71-77.

Martin, J. E. (2013). *Physics for radiation protection.* Ann Arbor, Michigan, United States of America: Wiley-VCH.

Matis, H. S. (2000, August 9). *Guide to nuclear wallchart*. (L. B. Lab, Editor) Retrieved from HSMatis@lbl.gov: http://www2.lbl.gov/abc/wallchart/chapters/03/3.html

NIST. (n.d.). Retrieved from NIST - National Institute of Standards and Technology : https://physics.nist.gov/PhysRefData/Star/Text/appendix.html

NIST. (n.d.). Retrieved from NIST - National Institute of Standards and Technology: https://physics.nist.gov/PhysRefData/Star/Text/ESTAR.html

NPL. (2006). *A National Measurement Good Pratic Guide N° 93 - Protocol for Establishing and Maintaining the Calibration of Medical Radionuclide Calibrators and ther Quality Control.* Teddington, Middlesex, UK: NPL.

Patel, S. B. (2011). *Nuclear Physics: an introduction* . New Deli : New Age International.

Santos, C. (2007, April). Basics of drug transport & delivery and radiopharmacy for nuclear medical. *REVISTA DO DETUA*, 787-789.

Southern Scientific. (n.d.). *Southern Scientific* . Retrieved from https://www.southernscientific.co.uk

Suzuki A., S. W. (1976). Analysis of a Radioisotope Calibrator. *Journal of Nuclear Medicine*, 193-198.

Tyler D. K., W. M. (2002). *NPL REPORT CRIM N°56, Syringe Calibration Factors and Volume Correction Factors for the NPL Secondary Standard Radionuclide Calibrator.* Teddington, Middlesex, UK : NPL.

Tyler D. K., W. M. (2002). *Syringe Calibration Factors and Volume correction factors for the NPL secondary standard radionuclide calibrator.* Teddington, Middlesex (UK): NPL.

Veenstra Instruments. (2012). *VIK - 202 USER MANUAL.*

Venstra Instruments. (2013). *VIK 203 USER MANUAL.*

World Nuclear Association. (2018, June). Retrieved from http://www.world-nuclear.org: http://www.world-nuclear.org/information-library/non-power-nuclear-applications/radioisotopes-research/radioisotopes-in-medicine.aspx

Yeong, C.-H., Cheng, M., & Ng, K.-H. (2014, October). Therapeutic radionuclides in nuclear medicine: current and future prospects. *journal of zhejiang university-science b*, 845-863.