SYNTHESIS OF THE PROJECT: PN-II-ID-PCE-2011-3-0070, Ctr. 23/05.10.2011

Absolute standardization and study of the decay data of the positron emitters used for PET systems. Assurance of the metrological traceability.

Project leader,
Dr. Maria Sahagia

Objectives of the project:

Development of a primary activity standard for the radionuclides produced and/or used in nuclear medicine in Romania for systems type Positron Emission Tomography (PET) and study of the decay scheme parameters.

The radionuclides proposed to be studied within the project are: ^{68}Ga, ^{18}F, ^{67}Cu and ^{124}I.

I-st stage. Study of the literature data for the radionuclide ^{68}Ga and its obtaining. 15.09.2011 - 15.12.2011

Proposed and accomplished objectives:

- **Study of the decay scheme data.** The most recent document published at that moment was: E. Schönfeld , file" $_{31}{}^{68}Ga_{37}$ " in *"Table de Radionucléides (ToR)"* ,1999, authors: M –M Bé et al. In 2013 the file was updated in: Table of Radionuclides Monographie BIPM-5 Volume 7 (BIPM -5/7), authors M –M Bé and E. Schönfeld

NOTE. Our paper A.Luca, M.Sahagia, A.Antohe. *Measurements of ^{64}Cu and ^{68}Ga half-lives and gamma-ray emission intensities*. Appl. Radiat. Isotopes 70, 9 (2012)1876-1880 is included in the reference list

- **Production of ^{68}Ga**. It can be directly produced at the cyclotron, or can be separated from a generator Ge-68(Electron Capture)Ga-68; ^{68}Ge is a cyclotron product.
- **Methods for absolute standardization of pure ^{68}Ga** . The 4πβ –γ coincidence method, using the existing installation in the Radionuclide Metrology Laboratory, is proposed. The general paper, treating the positron emitters standardization: **Grigorescu, E.L., Sahagia, M., Razdolescu, A., Ivan, C.** *Standardization of some electron capture radionuclides.* Nucl. Instr.and Meth in Phys.Res. A 369(1996) 414-420 is useful. It is also proposed to calibrate the ionization chamber, described in: **Sahagia, M., Wätjen, A.C., Luca, A., Ivan, C.** *IFIN-HH ionization chamber calibration and its validation; electrometric system improvement.* Appl. Radiat. Isot. 68(2010) 1266-1269

II-nd stage. Obtaining of the PET ^{68}Ga and ^{18}F standards. 16.12.2011 - 15.12.2012.

Proposed and accomplished objectives:

Obtaining of ^{68}Ga and ^{18}F, preparation of solutions and solid sources for standardization.

^{68}Ga was eluted from a ^{68}(Ge+Ga) generator. ^{18}F is in current production in Romania at the company Monrol Europe srl. Bucharest. It is under tests at the cyclotron TR 19, of the Radiopharmaceutical Research Centre of IFIN-HH. The reaction $^{18}_{8}O(p,n)^{18}_{9}F$ is used. For the present phase, a batch produced by the Monrol Europe srl. was used

Several rounds of preparation and measurement of solutions wereperformed, until the optimal solution was reached. The following operations were realized for both radionuclides: (i) preparation or conditioning of the concentrated solutions; (ii) preparation of the solutions for absolute standardization; (iii) preparation of a 5 ml vial and calibration of the CENTRONIC IG12/20A ionization chamber and precise determination of the half life; (iv) preparation of solid sources for absolute standardization and for gamma-ray spectrometry.

Absolute standardization by the 4π(PC)β-γ coincidence method in the variant of detection efficiency extrapolation and comparison with the gamma-ray spectrometry.

Radionuclide ^{68}Ga. The decay scheme is very complex, with the branching ratios (decay probabilities): a_1=0.8794(12); a_2=0.0120(3); a_3= 0.0179(4); a_4=0.0871(12); the coincidence relations are:

$$\frac{N_\beta}{N_o}=(a_1+a_2)\varepsilon_{\beta+}\{1+\frac{1}{a_1+a_2}\frac{1-\varepsilon_{\beta+}}{\varepsilon_{\beta+}}[(a_1+a_2)\varepsilon_{\beta 511}+a_2\varepsilon_{\beta\gamma}]+$$

$$\frac{1}{a_1+a_2}\frac{\varepsilon_{X,A}}{\varepsilon_{\beta+}}[a_3+a_4+a_3\frac{1-\varepsilon_{X,A}}{\varepsilon_{X,A}}\varepsilon_{\beta\gamma}]\};\frac{N_\gamma}{N_o}=(a_1+a_2)2\varepsilon_{511}[1+\frac{a_2+a_3}{a_1+a_2}\frac{\varepsilon_\gamma}{2\varepsilon_{511}}]$$

$$\frac{N_c}{N_o}=(a_1+a_2)\varepsilon_{\beta+}2\varepsilon_{511}\{1+\frac{a_2}{a_1+a_2}\frac{\varepsilon_\gamma}{2\varepsilon_{511}}+\frac{1-\varepsilon_{\beta+}}{\varepsilon_{\beta+}}[\frac{\varepsilon_{c511}}{2\varepsilon_{511}}+\frac{a_2}{a_1+a_2}\frac{\varepsilon_{c\gamma}}{2\varepsilon_{511}}]+$$

$$\frac{a_3}{a_1+a_2}\frac{\varepsilon_{X,A}}{\varepsilon_{\beta+}}[\frac{\varepsilon_\gamma}{2\varepsilon_{511}}+\frac{1-\varepsilon_{X,A}}{\varepsilon_{X,A}}\frac{\varepsilon_{c\gamma}}{2\varepsilon_{511}}]\}$$

N_0 = activity; N_β, N_γ, N_c =counting rates; $\varepsilon_{\beta r}$, $\varepsilon_{\beta\gamma r}$* = $\varepsilon_{\beta\gamma r}$, $\varepsilon_{\gamma r}$, $\varepsilon_{c\gamma}$, detection efficiencies.

The method was applied in two variants: (a) exclusive counting of the positrons in the proportional counter (PC) and of the annihilation radiations and of their coincidences; (b) counting of all emitted radiations.

Radionuclide ^{18}F. The decay probabilities are: a_1=0.9686(16); a_2=0; a_3= 0.0314(16); a_4=0. Only 511 keV, annihilation quanta, are emitted. X-rays and Auger electrons have <1keV energy and are not detected in the PC. Coincidence equations reduce at:

$$\frac{N_\beta}{N_o}=a_1\varepsilon_{\beta+}(1+\frac{1-\varepsilon_{\beta+}}{\varepsilon_{\beta+}}\varepsilon_{\beta 511});\frac{N_\gamma}{N_o}=a_1 2\varepsilon_{511};\frac{N_c}{N_o}=a_1\varepsilon_{\beta+}2\varepsilon_{511}(1+\frac{1-\varepsilon_{\beta+}}{\varepsilon_{\beta+}}\frac{\varepsilon_{c511}}{2\varepsilon_{511}})$$

Only the variant (a) was possible to be applied. The spectrometric measurements were done with the HPGe spectrometer, calibrated in energy and efficiency.

Table 1. Measurement results on the reference date

Activity concentrations	4π(PC)β-γ coincidences			Gamma-ray spctrometry (SG)	[SG -4π(PC)β-γ]/ 4π(PC)β-γ
	(a)	(b)	Mean (a) + (b)		
$(\frac{N_o}{m})_{Ga\text{-}68}, kBq\ g^{-1}$	27790±270	27560±190	27680±170	27900±600	+0.79%
$(\frac{N_o}{m})_{F\text{-}18}, kBq\ g^{-1}$	14824±77	-	14824±77	14300±430	-3.7%

Realisation of the secondary standard – calibration of the CENTRONIC IG12/20A

The efficiency ε_N , pA MBq^{-1} , was calculated initially from the decay scheme data and values determined for other radionuclides, and then it was determined experimentally, using standard solutions. The calibration factor, F , pA MBq^{-1}, is the ratio between the ionization current and activity.

Determination of the decay scheme parameters (half life and gamma-ray emission intensities)

Determination of half life, $T_{1/2}$. It was done with the ionization chamber CENTRONIC IG12/20A.

Table 2. Determined half life values and comparison with literature data.

Radionuclide	$T_{1/2}$ determined, (k=1)	$T_{1/2}$ according to literature	(IFIN-HH – literature)/ literature, %
^{68}Ga	(67.87±0.10) min, (k=1)	(67.83±0.20) min (BIPM -5/7),	+0.059
^{18}F	(1.8295±0.0005) h, (k=1)	(1.8288±0.0003) h. Table of radionuclides (ToR)	+0.038

Determination of the gamma-ray emission intensities. The determinations were made for the radionuclide ^{68}Ga, by gamma-ray spectrometry, with the HPGe detector. For ^{18}F this determination is not possible, as the branching ratio a_1=0.9686(19) is used in the calculation of the activity

Table 3 Emission intensities of gamma-rays for ^{68}Ga

	γ -ray emission intensities	
	This work: Absolute (per 100 decays)/Monographie (BIP-5/7)	Relative
511	(181 ± 6) / 177.8(8)	
578.5	(0.044 ± 0.010)/0.0343(23)	1.35(30)
805.8	(0.087 ± 0.011)/0.0928(27)	2.68(34)
1077.3	(3.25 ± 0.11)/3.235(30)	100
1261.1	(0.084 ± 0.009)/0.0954(21)	2.60(28)
1883.2	(0.128 ± 0.013)/0.1420(35)	3.94(42)

Use of standard solutions for the calibration of a commercial calibrator.

MONROL EUROPE srl company disposes of an ATOMLAB 500 BIODEX radionuclide calibrator, with the radionuclide ^{18}F included in its library. For the legal authorization of the production unit, in January 2012, our laboratory was required to certify the calibration done by the producer.

^{18}F was not available at that moment. We calibrated the instrument using a standard ^{68}Ga solution and the calibration factor of ^{18}F. Table 4 presents the calibration results.

Table 4 Calibration result

Radio nuclid	IFIN-HH certified activity/reference date	ATOMLAB 500 BIODEX measured activity	(ATOMLAB - IFIN-HH)/ IFIN-HH
^{68}Ga	(200.7 ± 6.0) MBq (k=2) /12.01.2012, 11:05 h	(188.3 ± 9.5) MBq	-6.2%

Published papers

1. M. Sahagia, A. Luca, A. Antohe, C. Ivan. *Standardization of ^{64}Cu and ^{68}Ga by the 4π(PC)β-γ coincidence method and calibration of the ionization chamber*. Applied Radiations and Isotopes,70,9(2012)2025-2030

2. M-M.Bé, P.Cassette, M-N. Amiot, M.C.Lépy, C.Bobin, K.Kossert, O.J.Nahle, O.Ott, C.Wanke, P.Dryak, G.Ratel, **M. Sahagia, A. Luca, A. Antohe**, L.Johansson, J.Keightley, A.Pearce.*Standardization, decay data measurements and evaluation of ^{64}Cu* . Applied Radiations and Isotopes, 70, 9(2012)1894-189

3. A. Luca, M. Sahagia, A. Antohe. *Measurements of ^{64}Cu and ^{68}Ga half-lives and gamma-ray emission intensities*. Applied Radiations and Isotopes, 70, 9(2012)1876-1880

4. M. Sahagia, A. Antohe, A. Luca, A. C. Wätjen, C. Ivan . „The Support Offered by the Romanian Primary Activity Standard Laboratory to the Nuclear Medicine Field",abstractnumber.doc2353248, Congress IRPA13, Glasgow, 2012, Proc., published in Rom. J.Phys.vol.58,nos.1-2(2013)106-116

III-rd step: Realisation of the national ^{18}F standard and preliminary measurements on ^{67}Cu, 16.12.2012 -15.12.2013

(i) Complete establishment of the Romanian ^{18}F standard

New solutions of ^{18}F were prepared and absolutely standardized and were used for the final calibration of the ionisation chamber. A number of 4 commercial radionuclide calibrators were calibrated; they belong to the following units: Monrol srl (1 piece), Euromedic SA, Bucharest (1 piece), IFIN-HH (2 pieces). The final results on the whole proces are included in the paper: **M. Sahagia*, R. Ioan, A. Luca, A. Antohe, C. Ivan, B. Neacsu, C.Ghioca**. *Standardization of ^{18}F and its use for the Romanian PET metrological traceability chain assurance*, presented at the Conference ICRM2013 (see ii.2)

(ii) Participation at the TRACE 2013 , IFIN-HH Workshop with a paper and at the International Conference ICRM 2013, Antwerp, Belgium, with two papers.

(ii.1) Within the period 03 – 05 April 2013, IFIN-HH, Radiopharmaceutical Research Centre, organized the workshop: TRACE – Development of New Radiotracers for PET Imaging and Targeted Radiotherapy, http://www.ifin.ro/events/conferences/trace/organizers

IFIN-HH and IAEA, Vienna. The oral paper p16 : **M. Sahagia, A. Luca, R. Ioan, A. Antohe, C.Ivan, B. Neacsu**. *Metrological traceability assurance in production and use of radiopharmaceuticals for PET imaging and targeted radiotherapy*, was presented in the session „Planning and medical radioisotope production facility", 03.04.2013

(ii.2) . Conference ICRM 2013: 19-th International Conference on Radionuclide Metrology and its Applications, ICRM 2013, Antwerp, Belgium, 17 – 21 June 2013, hosted by the European Commission – Joint Research Centre. Institute for Reference Materials and Measurements (IRMM). http://irmm.jrc.ec.europa.eu/icrm2013

This biennial conference is organized under the auspices of the International Committee for Radionuclide Metrology (ICRM), the world scientific forum in the field. The accepetd papers are peer reviewed by two independent reviewers and those meeting the standards for publications are published in a special issue of the journal: Applied Radiation and Isotope, Elsevier Editor, ISI Thomson quoted with relative influence score (SRI) =1.08857 (2012). Within the project, two papers were accepted and presented at the conference:

- The paper: **M. Sahagia*, R. Ioan, A. Luca, A. Antohe, C. Ivan, B. Neacsu, C.Ghioca**. *Standardization of ^{18}F and its use for the Romanian PET metrological traceability chain assurance.* Poster P#005 , directly refers at the ^{18}F metrological traceability chain.

- The paper : M.**Sahagia, A.Antohe, R.Ioan, A.Luca, C.Ivan.** *Standardization of Tc-99 by two methods and participation at the CCRI(II)-K2.Tc-99 comparison*. Poster P#004

It refers at the participation of the Radionuclide Metrology Laboratory in the key comparison organized under the auspices of the International Committee of Weights and Measures (CIPM), Consultative Committee for Ionising Radiations, Section II, Radionuclide Measurement [CCRI(II)], within the International Bureau of Weights and Measures (BIPM) Sèvres, France. The pilot laboratory was National Physical Laboratory (NPL), UK. The participation in key comparisons is the primordial condition for the demonstration of the international equivalence of the primary activity standards owned by the IFIN-HH, in its quality of Designated Institute for the field of ionising radiations and for he assurance of national traceability of measurements. Radionuclide ^{99}Tc is the daughter of ^{99m}Tc and is important both for nuclear medicine and for nuclear energetics (very long life waste, difficult to measure). It is a pure beta emitter with maximum energy 293.7 keV and $T_{1/2}$ =2.14 x 10^5 y and is used as reference mean energy pure beta radionuclide in calibration of contaminometers. Two independent methods were used for absolute standardization: Liquid Scintillation Counting- variant Triple to Double Coincidence Ratio (LSC-TDCR) and 4π(PC)β-γ coincidence , variant of efficiency tracer.

(iii). Study of literature data and preliminary measurements for standardization of radionuclides: ^{67}Cu and ^{124}I

(iii.1). Literature data regarding ^{67}Cu and ^{124}I.

Radionuclide ^{67}Cu.^{67}Cu is a beta gamma - emitter with a half life of 61.87 h (2.58 d), with a complex decay scheme of triangular type, resulting in a weak intensity and low energy 184.6 keV (48.7%) gamma-ray emission and strong emission of beta rays, maximum energy between (168.2 – 561.7) keV, intensity 100%. Its decay scheme was not studied intensely up to now, existing discrepancies between the published data (ToR. 2007), (NDS,2005), (Lederer et al.1967). It is important for use in nuclear medicine for targeted radiotherapy, especially in radioimmunotherapy: (a) It can be associated in the same type of molecule with the short half life, 12.701 h, PET radionuclide ^{64}Cu, resulting a theranostics radiopharmaceutical product. (b) It is superior to ^{131}I in radiotherapy, as it has a high tropism for some organs and less intense and energetic gamma rays, resulting in the diminution of detriment to the adjacent organs of the target volume. It can be produced in several ways: Cyclotron, via reactions: ^{68}Zn(p,2p)^{67}Cu; ^{67}Zn(d,2p) ^{67}Cu; ^{64}Ni(α,p) ^{67}Cu , nuclear reactor, via ^{67}Zn(n,p)^{67}Cu and at LINAC, via ^{68}Zn(γ, p)^{67}Cu. No literature data exist regarding its absolute standardization. Use of the 4π(PC)β-γ coincidence method is proposed.

Radionuclide ^{124}I. ^{124}I is a positron emitter (22.7%), in competition with electron capture (77.3%), $T_{1/2}$ =4.1760d; it emits annihilation, 511 keV (45.4%), and gamma-rays with energies within the interval 602.7 keV - 2700 keV, with a complex decay scheme, (NDS, Katakura and Wu, 2008). Only two papers were published on its standardization and decay scheme measurements (D.H.Woods et al.,1992) and (Qaim et al. 2007). Its use in nuclear medicine in diagnosis is favoured by: it is a PET variant for SPECT radionuclides ^{123,125,131}I, having a better resolution; it has a longer half life as compared with other PET nuclides ^{18}F, ^{11}C, allowing for a deeper investigation of the biochemical processes. ^{124}I is produced at cyclotron, via reaction: ^{124}Te(d,2n)^{124}I, when highest radionuclidic purity is reached. The coincidence method, type 4π(PC)β^+,X,Auger – γ, is proposed for absolute standardization.

(iii.2). Purchase of ^{124}I solution and preliminary measurements

^{124}I was purchased from ACOM Spa Advanced Center Oncology Macerata, Italy. The preliminary measurements regarded the following aspects:

Measurement of the ionization current in the chamber type CENTRONIC IG12/20A and evaluation of the total activity, based on the theoretical evaluation of the chamber response to ^{124}I. Preparation of the solid sources for absolute standardization, study of the spectra in the two measurement channels and record of counting rates; a preliminary evaluation of activity was done. The works will continue in 2014. At the same time, comparative measurements by gamma-ray spectrometry were performed, as well as with commercial calibrators, CAPINTEC and VENSTRA, existent in IFIN-HH, calibrated for ^{124}I by their producers. Table 5 presents the comparative results

Table 5. Preliminary results on standardization of ^{124}I, reference 24.10.2013, 12:00 h (UTC + 3)

Solution type	Evaluated efficiency of the chamber	Measured activity with CENTRONIC	Gamma spectrometry measured	Preliminary activity, 4π(PC)β^+,X,	Activity measured with	Activity measured with PET-

	CENTRONIC IG12/20A , pA/MBq	, MBq	activity, MBq	Auger – γ coincidence, MBq	CAPINTEC CRC 25R, MBq	VENSTRA, MBq
Concentrated solution, ampoule with 1.3 g of solution	33.45±1.00	112.5±3.4	-	-	116.14±5.8	105.7±5.3
Diluted solution, vial with 5 g of solution	33.28±1.00	38.91±1.20	40.98±1.60	39.89±1.20	-	-

Conclusions:
- The activity value of the concentrated solution measured with CENTRONIC IG12/20A chamber is situated between the values of the two commercial calibrators' results;
- The activity value of the diluted solution measured by coincidence is between those of the chamber CENTRONIC IG12/20A and of the spectrometer.

IV-th step: Publication of three papers. Standardisation of the radionuclide ^{124}I and establishment of the ^{124}I standard, 16.12.2013 -15.12.2014

(iv.1) Publication of two papers presented at the ICRM2013 Conference and of a paper at the Workshop TRACE

1.The paper: **M. Sahagia*, R. Ioan, A. Luca, A. Antohe, C. Ivan, B. Neacsu, C.Ghioca**. *Standardization of ^{18}F and its use for the Romanian PET metrological traceability chain assurance,* presented as Poster P#005 at the conference, supported the review process and was published in the Journal Applied Radiation and Isotopes, 87(2014)14 – 18, Section Life Sciences. www.elsevier.com/locate/apradiso

2.The paper : **M.Sahagia, A.Antohe, R.Ioan, A.Luca, C.Ivan.** *Standardization of Tc-99 by two methods and participation at the CCRI(II)-K2.Tc-99 comparison*. , presented as poster P#005 at the conference, supported the review process and was published in the Journal Applied Radiation and Isotopes, 87(2014)410 – 413, Section Intercomparisons www.elsevier.com/locate/apradiso

3.The paper: **M.Sahagia, A.Luca, R.Ioan, A.Antohe, C.Ivan, B.Neacsu**. *Metrological traceability assurance in production and use of radiopharmaceuticals for PET imaging and targeted radiotherapy,* presented as oral paper at the workshop TRACE, 2013, was published in the Romanian Journal of Physics, 59, 1-2 (2014)119-130, Section Medical Physics. www.nipne.ro/rjp

(iv.2) Standardisation of the radionuclide ^{124}I and establishment of the ^{124}I standard. Presentation of a paper at the Congress IRPA Europa, Geneva, 2014

The measurements done at IFIN-HH regarding the creation of a Romanian ^{124}I standard at the primary and secondary level regarded the following activities

1. **Absolute standardization by the 4πβ(PC)-γ coincidence method**.

^{124}I has a very complex decay scheme, with the following particularities. (a) Due to its high atomic number, Z = 53, the weight of electron capture over positron decays is high, P_{EC}/P_{β^+} = 3.41 and the energy of K Auger electrons and x rays is high, with the impulse spectrum in the PC overlapping the positron's one, so the counting of exclusively positrons, annihilation quanta and their coincidence is not possible. (b) It emits many gamma radiations, 602.7 keV- 2746 keV, strongly influencing annihilation rays detection. (c) The decay scheme is of the triangular type (23.9% electron captures to the ground level). Two previous papers were published: Woods et al.1992 (Applied Radiation and Isotopes (ARI).43,9,551) and Quaim et al.2007 (Radiochim. Acta 96,67). We used an alternative application of the 4πβ(PC)-γ coincidence method, based on counting the entire impulse spectrum, X,A and positrons, and measuring on different NaI(Tl) gamma-ray spectrum energy intervals, see also *Sahagia et al.* 2012(ARI.70,9,2025), in the variant of efficiency extrapolation. The particularities in application of the method are: the two efficiencies, $\varepsilon_{\beta+}$ and $\varepsilon_{X,A}$ do not reach the value 1.00 in the same time, and their ratio must be determined; the complex gamma ray spectrum influence over annihilation must be determined; the extrapolations cannot be done in full linearity condition accomplishment and the corrections must be calculated.

The basic treatment consisted in the following steps: an equivalent decay scheme was drawn and the corresponding general coincidence equations were written. The expressions for the value of extrapolation $\left(\frac{N_\beta N_\gamma}{N_c N_0}\right)_0$ were calculated within two independent treatments: general triangular scheme extrapolation and gamma-ray corrections over annihilation; a good agreement was reached. The practical measurements were done as: entire spectrum in the proportional counter and four gamma-ray settings: (i) (440-535) keV - basically annihilation, similar as Woods;(ii) (440-670) keV – annihilation and 603 keV; (iii) (440-1510) – closer to the approximate linear extrapolation; (1510-2015) keV for the determination of the X,A efficiency and its relation with that corresponding to positrons. The efficiency relation: $\varepsilon_{\beta+} = f(\varepsilon_{X,A})$ was experimentally determined from settings (i) and (iv) and gamma-ray corrections were determined using standard sources of ^{137}Cs and ^{60}Co. The activity N_0 was determined as the mean of the two calculations: general triangular scheme extrapolation and gamma-ray corrections.

The mean activity concentration was finally calculated as the weighted mean of the three values determined in the measurement conditions (i) – (iii), on the reference date and the combined standard uncertainty, u_c was considered as the internal uncertainty from the individual values, which contain also the correction components. The external uncertainty was only 0.65%

$$\left(\frac{N_0}{m}\right)_{I\text{-}124} = (8979 \pm 117)\ \text{kBq g}^{-1}; u_c = 1.30\%,\ k = 1$$

2.Calibration of the CENTRONIC IG12/20A ionization chamber. The calibration factor *F*, pA MBq^{-1}, was determined with the standardized solution, for various recipients. The **theoretical evaluation of the chamber efficiency**, E_N, from other radionuclides was difficult due to higher energy quanta and on this purpose the data from ^{124}Sb calibration were used. The preliminary evaluated chamber efficiency, E_N =(33.28±1.00) pA/MBq, reported in Table 5, was corrected by taking into account the revised individual contributions of the high energy gamma rays, arriving to the new value E_N =(32.65 ± 1.32) pA/MBq, a value in agreement with the

former one, within the limit of uncertainties. The activity concentration, calculated using this efficiency value was determined as: $(\frac{N_0}{m})_{\text{I-124,IC}} = (8831 \pm 353)\ \text{kBq g}^{-1}; u_c = 4.0\%,\ k = 1$

On the other hand, using the value of the activity concentration, measured absolutely by coincidence method (point 1), a primary method, the **experimental calibration of the chamber** and the transfer of the activity unit from the primary to the secondary standard was performed, assuring the metrological traceability chain. The calibration factor is F = (32.11±0.45) pA/MBq, a value more precisely determined, which differs only by 1.68% from the new evaluated E_N

3. Gamma spectrometry measurements. The activity and radionuclidic purity were determined with the calibrated HPGe spectrometer, using standard sources prepared in the laboratory. No impurities, with a contribution higher than 0.01% from ^{124}I activity were detected in solution. The determined activity concentration was: $(\frac{N_0}{m})_{\text{I-124},\gamma} = (9128 \pm 356)\ \text{kBq g}^{-1}; u_c = 3.9\%,\ k = 1$

4. Comparison of methods. The coincidence result is situated between those of ionization chamber and gamma-ray spectrometry; all the differences are within the calculated uncertainties, k=1. Table 6 presents these results.

Table 6. Comparison of measurement methods

Method	4πβ(PC)-γ coincidence (CO)	Ionisation chamber (IC)	γ-ray spectro (γ)	Differences
$(\frac{N_0}{m})_{\text{I-124,}}$ kBq g^{-1} ± u_c	8979 ± 117 (1.30%)	8831±353 (4.0)%	9128±356 (3.9)%	(IC-CO)/CO = - 1.65% (γ – CO)/CO= + 1.66% (IC - γ)/ γ = - 3.25%

This result of Table 6 reconfirms the preliminary measurement result, presented in Table 5: the coincidence result is situated between ionisation chamber evaluation and gamma-ray spectrometry measurement.

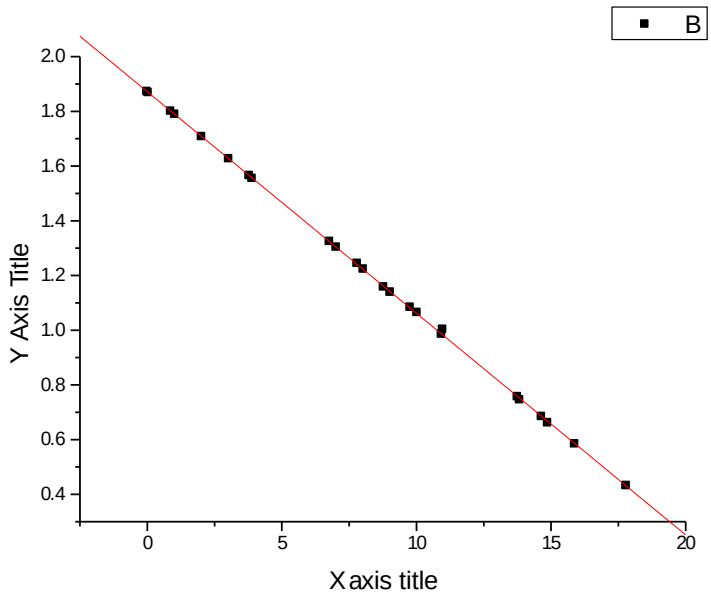
5. Measurement of the decay scheme parameters.

- The **emission intensity** of the main gamma rays was measured using standard solid sources prepared from standard solution. The main full absorption peaks: 511 keV; 602.7 keV; 722.68 keV and 1691.02 keV were registered and their emission intensities were determined as ratios between counting rates, s^{-1}, efficiency and activity, Bq; the final calculations are on way.

- The **half life** was measured with the ionization chamber. A vial containing 5 ml of solution was measured for a 18.04 days (4.32 half lives) period, obtaining 25 experimental points. The ionization current values were calculated as means of 10 readings and the background was subtracted; it varied between 661.4 pA and 33.07 pA. No impurity level higher than 0.0001 was found. The determined value of the half life from the fitting of data was:

$T_{1/2}$ = (4.1758±0.0014) d.

Uncertainty budget: Statistical uncertainty of the fitting: u_A=0.0012 d; uncertainty due to background: u_B = 0.0007 d. The determined value differs from the published one [$T_{1/2}$=(4.1760±0.0003) d] by [- 0.0002 d (- 0.008)%] . The decay graph is presented in Figure 1.



Presentation of a paper at the Congress IRPA Europa, Geneva, 2014

The paper. **M. Sahagia, M-R. Ioan, A. Antohe, A. Luca, C. Ivan.** *Measurement of positron emitting radionuclides' activity and their use for the calibration of the PET calibrators*, was presented as Poster at the Fourth European IRPA Congress, *Radiation Protection Culture – A global challenge*, Geneva, Switzerland, June 23-27, 2014. The full text was published as Extended Abstract.PS 5-4, in the Section Dosimetry & Measurement, number 36, pages 279 – 282, in the Abstract Book, updated version 02.07.2014. http://www.irpa2014europe.com.

It was also introduced in **Radiation Protection Dosimetry (2015), Vol. 164, No. 1–2, pp. 179–180 doi:10.1093/rpd/ncv288. FOURTH EUROPEAN IRPA CONGRESS 23–27 June, 2014 – Geneva, Switzerland AUTHOR INDEX, Sahagia, M. 176**

Presentation of a paper at the 5th Workshop of the Decay Data Evaluation Project (DDEP-2014) October 6-8, 2014 - Bucharest-Magurele, Romania.

The paper. **M. Sahagia, A.Luca, A. Antohe, M-R. Ioan, C.Ivan.** *Recent work and results of the radionuclide metrology laboratory from IFIN-HH* **,** was presented as Invited Lecture at the workshop; it included the main results obtained within the project. The paper in accepted for publication at Romanian Reports in Physics, in press, November 2015.

V-th Step: Presentation of a paper at the Conference ICRM 2015, Vienna, 16.12.2014 – 15.12.2015

Planned activities: Drawing up of the first draft of the paper, according to the ICRM 2015 reviewers' requirements

1. Participation at the la Conference ICRM 2015, www.icrm2015.boku.ac.at

During the period 8 -12 June 2015, the ICRM2015 „20-th International Conference on Radionuclide Metrology and its Applications", organized by the International Committee of Radionuclide Metrology (ICRM), took place at the Technical University Vienna, Austria. Two papers were presented:

- Poster #P013: [1]. M. Sahagia*, M-R. Ioan, A. Antohe, A. Luca ***„Measurement of ^{124}I,"*** paper entirely supported from the Project, was presented at the session „**Radionuclide Metrology Techniques**"

- Poster #P039: [2] A. Luca*, M. Sahagia, M.-R. Ioan, A. Antohe, B. L. Neacsu***, „Experimental determination of some nuclear decay data in the decays of ^{177}Lu, ^{186}Re and ^{124}I"***, was presented at the session: „**Nuclear Decay Data"** ; the section regarding radionuclide ^{124}I was supported from this Project. Data for ^{177}Lu anf ^{186}Re were part of the Project IFA Romania – CEA France no. C2-05/2012.

Both papers were revised by two referees and discussed with the corresponding authors during the Conference and were transmitted by the Secretary of the Scientific Committee in the final form, to the journal Applied Radiations Isotopes, to be published during 2016. Both papers have the mention: **" Acknowledgement**. This work was supported by a grant of the national research project CNCS, UEFISCDI, PN-II-ID-PCE-2011-3-0070".

2 Other work accomplished within the V-th Step.

2.1 Scientific Referee and Representative of IFIN-HH in ICRM .

- Dr. Maria Sahagia served as scientific referee for two papers presented at the Conference ICRM2015, Section: Aspects of the International Metrology & Intercomparisons: (i) Paper O#45: C.Michotte et al. „*Comparison of ^{18}F activity measurement at VNIIM, NPL and ENEA using the SIRTI of the BIPM"*; (ii)Paper P#143: P.Cassette et al. „*Activity comparison between CPST, VNIIM and LNHB* "
- Dr. Maria Sahagia is the designated representative of IFIN-HH in the International Committee of Radionuclide Metrology (ICRM) and in this quality she participated at the ICRM General Meeting, BEV, Vienna, on 12.06.2015.

2.2 Measurement of ^{18}F (Fluorodeoxyglucose) produced at the Cyclotron TR 19 of the Radiopharmaceutical Research Centre (CCR), IFIN-HH, and calibration of the equipment used for the measurement of obtained at cyclotron ^{18}F activity .

A cyclotron TR 19 produced ^{18}FDG(fluorodeoxyglucose) vial was prepared and standardized using the Ionisation Chamber CENTRONIC IG12/20A. The chamber had been calibrated using a standard ^{18}F solution absolutely measured, by the 4πβ(PC)-γ method. In this manner, the Project motivation, declared at the Point C4 of the financing request „*C4. Impact, relevance, applications* was fulfilled. The calibration Certficate no. 12556/25.03.2015, for the batch F-18@23.03.2015, with conventionally true vial activity, A=(1052±32) MBq, on reference date, was issued. This standard vial was further used to calibrate four radionuclide calibrators used within the ^{18}F production line. Table 7 presents the results.

Table 7 Calibration of the CCR,IFIN-HH, radionuclide calibrators

Calibrator	Pitagora 008 IC8B/337	Pitagora 008 IC 20A/181	Talete 0090 IC8A/333	Veenstra VDC-405 21111-5051-07
No. Calibration Certificate	12560/25.03.2015	12559/25.03.2015	12558/25.03.2015	12557/25.03.2015
Deviation of the calibrator indicated activity vs. conventionally true value	-4.8%	-7.0%	-4.9%	-0.4%

2.3 Calibration of radionuclide calibrators from nuclear medicine units

Another objective of the point C4 was: „*The metrology traceability chain will be established to the hospitals applying these techniques"* LMR performs already the calibration of the calibrators used in Romanian PET medical units for radionuclide ^{18}F. A ^{18}FDG solution, a MONROL EUROPE srl product, was standardized and the Calibration Certificate no. 12590/24.06.2015 was issued. The activity was A =(4.314± 0.086) GBq on reference date. Table 8 presents the 2015 obtained results.

Table 8 Calibration of medical units' calibrators

Calibrator	CAPINTECCRC25PET PR.CAL.02_270460, MONROL EUROPE srl	CAPINTECCRC25PET PR.CAL.02_270395, MONROL EUROPE srl	CAPINTEC CRC55tR MNT Healthcare Europe SRL
No.Calibration Certificate	12591/24.06.2015	12592/24.06.2015	12596/03.07.2015
Deviation of the calibrator indicated activity vs. conventionally true value	+1.1%	+1.1%	-3.6%

General observations

- All the radionuclide calibrators, from IFIN-HH, CCR, and from other units, meet the requirement for uncertainty limit: ±10%.

- The activities measured with commercial calibrators are both higher and lower than LMR reference values, what demonstrates the good quality of the performed calibrations.

3. Publications within V-th step.

Two papers were presented at the ICRM2015 Conference; they follow to be published in an ISI Thomson quoted journal

[1]. M. Sahagia*, M-R. Ioan, A. Antohe, A. Luca „*Measurement of ^{124}I*," ICRM Conference, Vienna, Austria, 2015

[2]. A. Luca*, M. Sahagia, M.-R. Ioan, A. Antohe, B. L. Neacsu *„Experimental determination of some nuclear decay data in the decays of ^{177}Lu, ^{186}Re and ^{124}I",* ICRM Conference, Vienna, Austria, 2015

VI-th step „Standardization of ^{67}Cu sand establishment of the ^{67}Cu standard"
16.12.2015 – 4.10.2016

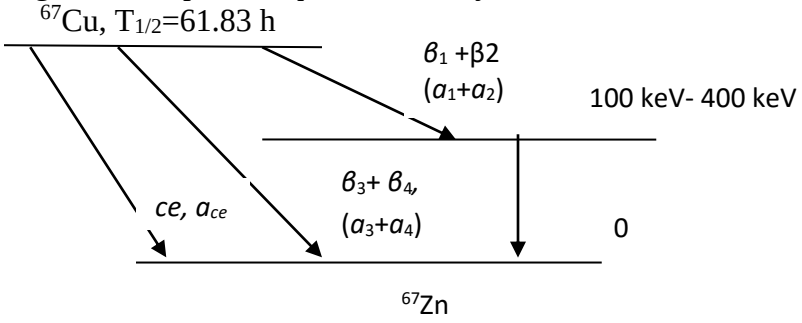
Activities (i) Purchase and standardization of a ^{67}Cu solution: Absolute standardization; (ii) Characterization of the solution and calibration of the ionization chamber.

One experimental batch was purchased from the Nuclear Physics Institute AS CR, v.v.i, Department of radiopharmaceuticals, 250 68 Husinec-Rež 130, Czech Republic, under responsibility of Dr. Ing. Ondřej Lebeda. The solution has the chemical composition: Cu-67 in HCl solution, valence (+2), as $CuCl_2$.

On the receipt of the vial, the first measurement of the radioactive concentration was performed, using a calculated efficiency of ^{67}Cu. The first operation with the solution was the preparation of five solid sources from the original solution, on golded VYNS foils, which were left to dry and then were redissolved with LUDOX 10^{-4} , what improved significantly the counting efficiency in the 4πsr proportional counter, from 0.70 until 0.80. In the same time, a penicillin vial, type P6, was prepared, with solution, for the calibration of the CENTRONIC IG12/20A ionization chamber, which will serve as a transfer instrument of the activity from the primary to working standards. The vial contained 1.77087g of solution, absolutely standardized, and 3.3950 g 1N HCl solution, in total 5.0659 g.

1. **Absolute standardization of the solution.** No literature reference regarding ^{67}Cu standardization at international level was found. The 4πβ(PC)-γ, coincidence method was used, taking into account that this radionuclide is a beta-gamma emitter. The 4πβ(PC)-γ coincidence installation, consisting from a proportional counter (PC) and a gamma-ray detector, was used. The radionuclide disintegrates by beta decays and gamma transitions, having a triangular scheme. A particularity is that the ^{67}Zn excited level of 93.31 keV suffers an isomer transition with the life time of 9.10μs, 93.31 keV gamma-ray emission being concurrent with emission of conversion electrons with energies: E_{ck} = 83.562keV, [I=0.1209(15)] si E_{cL} = 92.117 keV,[I=0.01481(18)]. This is why it is necessary to avoid the counting of the 93.31 keV on the gamma-ray channel, what was achieved by imposing a discrimination threshold higher than 100 keV; the upper limit was established at 400 keV. The decay scheme, as published by H. Junde, H.Xiaolong, J.K.Tuli. Nuclear Data Sheets 106(2005)159, ^{67}Cu file, was processed, obtaining a simplified equivalent scheme, such as presented in Figure 1.

Figure 1. Simplified equivalent decay scheme of ^{67}Cu



According to this scheme, the general coincidence equation is:

$$N_0 = \left(\frac{N_\beta N_\gamma}{N_c}\right)_{extrapolated} \frac{1}{1+0.297\frac{0.8429+0.0025}{1.8429}} = \left(\frac{N_\beta N_\gamma}{N_c}\right)_{extrapolated} \frac{1}{1.1362} \quad (12)$$

From relation (12) one can be observed that we must apply a corrective factor f = (1.1362±0.0066), to the measurement data, due to conversion electrons non coincident with beta radiations.

Ch**aracterization of the solution was** done by the control of the radionuclidic purity using the high resolution gamma-ray spectrometry. A ^{67}Ga impurity an electron capture –gamma emitter, in a proportion of p = (3.59±0.91) % from ^{67}Cu activity was found. As both radionuclides decay to the daughter nuclide ^{67}Zn, a compound decay scheme was imagined and the corresponding calculations were performed, such as equation (12) becomes (16), for the calculation of the net ^{67}Cu activity.

$$N_0 = \left(\frac{N_\beta N_\gamma}{N_c}\right)_{extrapolated} \frac{1}{1.1510} \quad (16)$$

Other detected impurities were: ^{69}Ge proportion 0.005%, and ^{68}Ga, 0.10%, both of them neglected.

Table 1 presents the measurement results and the calculation of individual sources activities, N_0, Bq, as well as the massic activity (activity concentration) of the solution, $a=N_0/m$, kBq/g, in the two distinct situations: neglecting of impurities, relation (12), and performing impurity correction, relation (16) . One can be observed that the difference between the two results is only 1.3%, due to the small contribution of ^{67}Ga x and Auger radiations, in the proportional counter. The uncertainty due to the impurities is 0.56%.

Table 1 Measurement results on the reference time

Source	m,mg	$N_\gamma/N_c - 1$, no of points	$1 - K$	$(N_\beta N_\gamma/N_c)$ extrapolated	N_0, Bq, rel (12)	$a=N_0/m$, kBq/g, (12),	N_0 , Bq, rel (16)	$a=N_0/m$, kBq/g, (16)
W276	26.231	0.33 -0.67, 4p	0.0796	5452.2	4798.5	182.93	4736.8	180.58
W235	38.589	0.28–1.09, 4p	0.0716	8043.7	7079.2	183.45	6988.3	181.10
W090	37.778	0.3 -0.90,4p	0.100	7823.1	6885.0	182.25	6796.6	179.91
W323	34.785	0.31–0.65, 4p	0.0723	7174.8	6314.3	181.52	6233.4	179.20
W309	28.879	0.21–0.89, 6p	0.110	5964.9	5249.7	181.78	5182.3	179.45
Z19	34.900	0.27 -0.83, 4p	0.113	7225.0	6358.7	182.20	6277.0	179.85
Mean values			0.0910 ± 0.0076			182.36 ± 0.29 (0.16 %)		180.02 ± 0.29 (0.16 %)

2. Influence of the new published decay scheme parameters over activity.

In the paper: J.Chen, F.G. Kondev, I. Ahmad, M. P. Carpenter, J. P. Greene, R. V. F. Janssens, S. Zhu, D. Ehst, V. Makarashvili, D. Rotsch, and N. A. Smith. *Precise absolute γ -ray and β−-decay branching intensities in the decay of 67,29Cu.* PHYSICAL REVIEW C 92, 044330 (2015) there are presented much different values of the decay parameters, as compared with the NDS. Calculations were performed in order to evaluate which is the influence of their change. Only an influence due to the intensity of 93.31 keV gamma-rays and of the conversion electrons exists, which can induce a supplementary uncertainty of 0.58%. **Uncertainty budget of the activity concentration** consists of: statistical component (0.16%), the two important components impurity (0.56%) and decay scheme parameters (0.97%, respectively 0.58%, depending on the internal conversion coefficient α_3) and other smaller components, arriving at a standard combined uncertainty of u_c = 0.85% (k=1). The final result is: **$a_{Cu\text{-}67}$ =[180.02± 1.53 (0.85 %)] kBq/g, (k=1) on reference time..**

3. Calibration of the CENTRONIC IG12/20A ionization chamber

Initially the values of detection efficiencies of the chamber were calculated from the existing data for other measured radionuclides. The calculated ^{67}Cu efficiency has the values:

(i) According to the decay data from NDS (Junde et al. ,2005)

$$E_N = (5.971 \pm 0.179)\, pA/MBq \quad (16)$$

(ii) According to the decay data (Chen et al., 2015)

$$E_N = (5.449 \pm 0.179)\, pA/MBq \quad (18)$$

Experimental value of the calibration factor, F.

Taking into account the ^{67}Ga impurity content there was necessary to operate a correction on the experimental value of the calibration factor. The relation for calculation of the efficiency is:

$$I = F_{Cu-67} A_{Cu-67} [1 + (F_{Ga-67} / F_{Cu-67})(A_{Ga-67} / A_{Cu-67})] \approx F_{Cu-67} A_{Cu-67} [1 + (E_{N\,Ga-67} / E_{N\,Cu-67})(A_{Ga-67} / A_{Cu-67})] \quad (20)$$

The detection efficiency for ^{67}Ga was calculated as:

$$E_N = (7.356 \pm 0.221)\, pA/MBq \quad (21)$$

Applying the corrective relation (20), the experimental value of the calibration factor for ^{67}Cu is:

F = (5.751 ± 0.063) pA/MBq (22)

Comments on the differences between the factor F and efficiencies E_N. (i) As compared with the NDS values, the difference is (F - E_N)/F = - 3.8% , almost at the uncertainty limit, but for the data from (ii) Chen, (2015) the difference is in opposite sense, +5.3%, what demonstrates that the calibration was proper. The conclusion is that the impurities and decay data have an important influence over the measurements performed with the ionization chamber.

4. Publications within the VI-th step.

The two papers presented at ICRM2015 Conference were published in March 2016, in Applied Radiation and Isotopes, an ISI Thomson quoted journal

- M. Sahagia*, M-R. Ioan, A. Antohe, A. Luca „*Measurement of ^{124}I*" Appl. Radiat Isot 109(2016)349-353

- A. Luca*, M. Sahagia, M.-R. Ioan, A. Antohe, B. L. Neacsu *„Experimental determination of some nuclear decay data in the decays of ^{177}Lu, ^{186}Re and ^{124}I"* . Appl. Radiat. Isot. 109(2016)146-150

Both papers mention in"**Acknowledgements**. This work was supported by a grant of the Romanian National Authority for Scientific Research, CNCS – UEFISCDI, project number PN-II-ID-PCE-2011-3-0070'

- M.Sahagia, A.Luca, A.Antohe, M-R.Ioan, C.Ioan. *Recent work and results of the radionuclide metrology laboratory from IFIN-HH*.Rom. Rep. in Phys. 68 No.1,(2016)177-190, paper partially supported from the project

An abstract entitled :" *Standardization of ^{67}Cu and calibration of the ionization chamber. Impurities and decay scheme problems*", authors: M. Sahagia*, A. Luca, M-R. Ioan, A. Antohe, C.Ivan , was sent to the 21-st International Conference on Radionuclide Metrology and its Applications, ICRM2017, Buenos Aires, Argentina.

Other activities deployed within the step VI-th. During the year 2016, the calibration of some ^{18}F solutions, from batches produced at IFIN-HH and at Monrol Europe srl., and of PET calibrators continued successfully. There were calibrated: IFIN-HH, Centre of Radiopharmaceutical Research (4 pieces), Monrol (3 pieces) and of Nuclear Medicine Centre throughout the country (3piees), The main objective of the project, Assurance of national traceability for PET radionuclides was accomplished.

CONCLUSIONS REGARDING THE ACCOMPLISHMENT OF THE PROJECT

The project had as a study object a number of four radionuclides applied in nuclear medicine: three positron emitters used in Positron Emission Tomography (PET): ***^{68}Ga, ^{18}F and ^{124}I,*** and a beta-gamma emitter ***: ^{67}Cu*** for therapy (Targeted/Molecular Radiotherapy) .
All the objectives of the project were accomplished, and supplementary activitiea were achieved.

1 . The primary national standards were established for all the four radionuclides:

1.1 The solutions prepared from all the four radionuclides were absolutely standardized, by the $4\pi\beta(PC)$-γ coincidence method;

1.2 The nuclear decay data were studied;

1.3 The CENTRONIC,IG20/20A ionization chamber, secondary standard for gamma-ray emitters, was calibrated for all the four radionuclides;

1.4 The entire national metrological traceability was assured: primary standard, secondary standard, measurement equipment belonging to the users, calibrated for the currently used radionuclides: ^{18F} and ^{68G}a.

2. Papers were published in ISI-Thomson quoted journals and presented at International Conferences. These publications were the result of the novelty and difficulty of the subject, which needed to find original solutions for absolute standardization, the subbject of published papers with a high degree of originality

2.1 A number of 10 papers were published: 7 papers in the journal Applied Radiation and Isotopes (Elsevier) and 3 articles in Romanian Journal of Physics and Romanian Reports in Physics (Romanian Academy)

2.2 A number of 7 papers were presented at International Congresses, Conferences, Workshops ; an abstract was submitted for the International Conference ICRM2017.

3 **The project leader and a member of the team** were recognized as international experts in Radionuclide Metrology and served as reviewers within the Conference ICRM2015, Vienna.