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MEASUREMENTS OF IONIZING RADIATION

^{68}GA UNIT OF ACTIVITY: TRACEABILITY TO THE RUSSIAN NATIONAL PRIMARY RADIONUCLIDE ACTIVITY STANDARD

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Questions on the use of the radionuclide ^{68}Ga in the medical institutions of the Russian Federation for diagnosis of malignant tumors were examined. The task of precise measurement of ^{68}Ga activity in order to decrease dose loads for patients and enhance the effectiveness of the diagnosis is very important. Calibration of the mobile RIS-3A reference dose calculator to ^{68}Ga activity was studied. Various methods of calibration, ensuring traceability to the National Primary Standard of the units of radionuclide activity, the specific activity of radionuclides, and the stream of alpha and beta particles and photons of radionuclide sources in GET 6-2016 are: the method of direct comparison with a UÉA-7 installation from GET 6-2016, using a sample of ^{68}Ga solution; and the use of a gamma spectrometer and sources based on other radionuclides with traceability of the unit of radionuclides to GÉT 6-2016. The expanded uncertainty budgets of the calibration coefficient are presented for both calibration procedures, using the UÉA-7 installation from GET 6-2016, and a gamma spectrometer with ^{18}F. The convergence of the measurement results of ^{68}Ga activity on the reference dose calibrator, with calibration coefficients obtained by different methods, was evaluated. The results obtained confirm the applicability of the various calibration methods. The results of the study may find application in ensuring the traceability to GET 6-2016 of the units of activity of other promising radionuclides introduced into medical practice.

Keywords*: radionuclide activity, primary standard, calibration.*

Introduction. Gallium is a light metal, an element of the 13th group of the periodic table, with atomic number 31. Gallium has 31 known isotopes, of which the one of greatest interest for medicine is the radioactive isotope ^{68}Ga. With high probability (87.68% [1]), ^{68}Ga undergoes β^+ decay with positron emission. As a result of its rather short half-life (67.83 min [1]), this radionuclide is suitable for positron emission tomography. In the process of developing positron emission tomography, the greatest popularity in medical applications was from the short-lived ^{11}C and ^{18}F, which are easily inserted into organic molecules. Currently, the increasing interest in ^{68}Ga is associated with the broad therapeutic application of radioactive metals. ^{68}Ga perfectly achieves the role of a concomitant diagnostic radionuclide when paired with the radioactive therapeutic metal ^{177}Lu. In the process of the chelation reaction, the radioactive isotope ^{68}Ga can mark the transport molecules or antibodies that are applied in diagnosis of oncological diseases. Radiopharmaceutical medicines based on ^{68}Ga are used for diagnosis of neuroendocrine tumors and oncological diseases of the prostate [2–4].

The importance of the radionuclide ^{68}Ga is reinforced by a relatively high degree of accessibility. The market has commercial generators based on ^{68}Ge [sic]. The procedure for obtaining ^{68}Ge [sic] in cyclotrons was standardized by the International Atomic Energy Agency (IAEA) [5] and is widely and successfully applied. Domestic generators of ^{68}Ga

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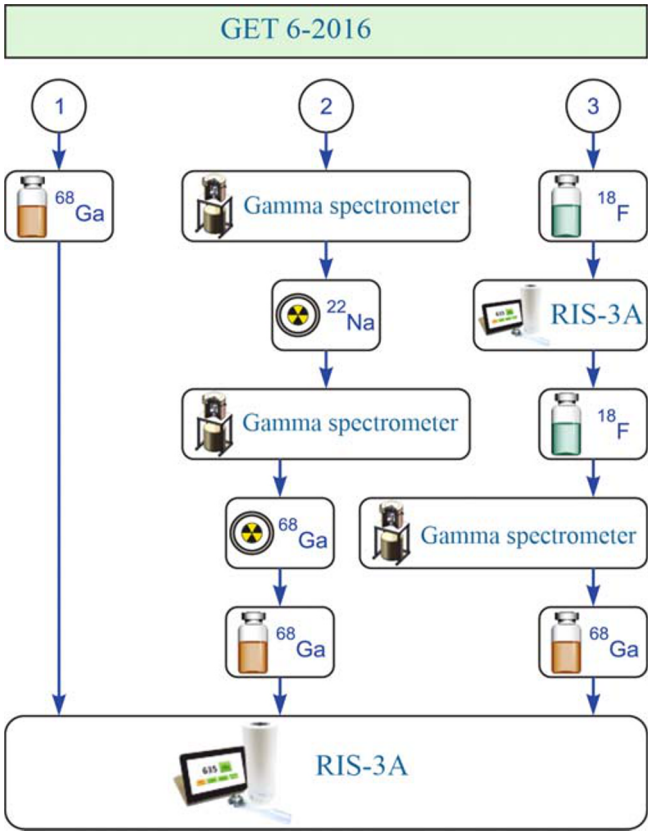

Fig. 1. Traceability of the radionuclide unit of activity to GET 6-2016: 1) calibration using the UÉA-7 from GET 6-2016; 2, 3) calibration using a gamma spectrometer and ^{22}Na and ^{18}F, respectively.

(Closed Joint Stock Company Tsiklotron, Obninsk) and specialized radiochemical safety boxes for operation with them (STC NTTs Amplituda LLC, Zelenograd). are available in Russia.

In accordance with the requirements of legislation in the field of the provision of the unity of measurements, measurement facilities for the activity of radiopharmaceutical medical preparations must have traceability to the National Primary Standard of the units of the activity of radionuclides, the specific activity of radionuclides, and the flow and flow density of alpha and beta particles and photons from radionuclide sources by GET 6-2016. The primary means for measuring the activity of radiopharmaceutical medicines is a radiometer of radionuclide activity (a dose calibrator), which is an ionization chamber of a well type, inside which the flask or injector with the radiopharmaceutical preparation is placed. The mobile reference dose calibrator is used for verification and calibration of the dose calibrators of medical institutions.

A feature of the measurements of the unit of radionuclide activity is its specificity for each radionuclide. This is caused by the fact that the number of decays per second in a sample, i.e., the activity of a sample in becquerels, is measured by recording the emission originating in the decay process, and the characteristics of the emission are specific to each radionuclide. As of now, several hundred different radionuclides are known, and only a small part are the ones most demanded in industry and science and measured by GET 6-2016. The rapid development of radio pharmacology in recent decades evokes calls for radionuclide metrology. New short-lived radionuclides are regularly introduced into clinical practice with a half-life ranging from several minutes to several days. The measurement of the activity of these short-lived radionuclides by GET 6-2016 and subsequent calibration of a reference dose calibrator cause difficulties as a consequence of the necessity of rapid delivery of the radionuclide from the production site to the place of measurements. In special cases, it is possible to use complex schemes for calibrating a reference dose calibrator, in order to ensure traceability to GET 6-2016. Radionuclides undergoing β+ decay with emission of a positron in the gamma spectrum of which an annihilation line 511 keV is present are such a special case. It is possible to transfer the unit of activity from one β+-decaying radionuclide, for which the unit of activity is traced directly to GÉT 6-2016. to another β+-decaying radionuclide for which the unit of activity of such traceability is not present.

We examine the following methods of calibrating a reference dose calibrator [6]: the method of direct comparison with an installation from the GET 6-2016 formulation using a sample of ^{68}Ga solution; or using a gamma-ray spectrometer and sources based on other radionuclides that have traceability of the unit of activity of the radionuclides to GET 6-2016.

Figure 1 shows the chains of metrological traceability to GET 6-2016 measurement results of ^{68}Ga activity on a reference dose calibrator: 1) calibration by means of a UÉA-7 installation from the GET 6-2016 formulation; 2, 3) calibration using a gamma-ray spectrometer and ^{22}Na and ^{18}F, respectively.

The objective of this article is to present the results of various methods of calibrating the RIS-3A reference dose calibrator on ^{68}Ga activity and compare the activity measurement results for ^{68}Ga to the reference dose calibrator with the calibration coefficients obtained by different methods.

Calibration by a UÉA-7 installation from the GÉT 6-2016 formulation. One difficulty of the calibration of a reference dose calibrator by ^{68}Ga activity using an installation from a formulation of GET 6-2016 is the short half-life (67.83 min [1]), and the great transportation time of a radiopharmaceutical preparation from the production site to the location of measurements. After the appearance of a ^{68}Ga generator in St. Petersburg and, correspondingly, the reduction of transportation time, work was done on calibrating the reference dose calibrator by means of an installation from the GET 6-2016 formulation.

For the calibration, a hermetically sealed 10 ml flask containing 4.83 g of ^{68}Ga solution was measured. The specific activity of ^{68}Ga in the solution was measured on a UÉA-7 installation from the formulation of GET 6-2016 [7], implementing the absolute 4πγ-counter method, designed for measurement of the activity of gamma-emitting radionuclides.

The detection device of the installation was made from two scintillation detectors with NaI (TI), of diameter 200 mm and height 100 mm. In order to implement the 4π-geometry, the radionuclide source being measured is placed in a well with diameter 42 mm and depth 10 mm, made in one of the detectors. To decrease background noise, the detectors are protected by a copper housing. In the measurement of radionuclide activity, the energy of the photons of the source is almost completely absorbed in the material of the crystals and is converted into scintillation energy — luminous flashes that are recorded in the photoelectric amplifier. The size of the crystals is selected in such a manner as to ensure high effectiveness of the recording of photons with energy up to 2 MeV.

The measurement channel of the installation consists of an NIM chassis with modules, a computer, and an uninterruptible power supply. Signals from the detector units arrive at the measurement channel, and are amplified and digitized using the N6720B digitizer from CAEN (Costruzioni Apparecchiature Elettroniche Nucleari S.p.A., Italy). The digitized signal travels along the optical data transfer main line to the computer for subsequent processing.

A load in the form of an Eppendorf test tube 0.2 mL with an aliquot ^{68}Ga solution of mass 0.098 g was used for the measurements. The unit of specific activity of a radionuclide (the becquerel, Bq) on the installation is reproduced according to the formula

$$A_{\text{sp}} = (n - n_{\varphi})/(m\eta),$$

where n is the counting rate of pulses from a radionuclide source; n_{φ} is the counting rate of background pulses; m is the mass of the aliquot; and η is the sensitivity of the installation, determined for photon emission of ^{68}Ga by numerical modeling methods (Monte Carlo method).

Table 1 presents the uncertainty budget for calibration by means of a UÉA-7 installation and weights from the formulation of GET 6-2016, where $u(x_i)$ is the relative standard uncertainty, u_s is the total relative standard uncertainty (the root of the sum of squares of all terms), and u_e is the relative extended uncertainty with spanning coefficient k.

Calibration using a gamma-ray spectrometer and ^{22}Na. The activity of a sample of ^{68}Ga can be determined by comparison with a radionuclide source of known activity, made of another radionuclide: a positron emitter using a gamma-ray spectrometer as the comparator for the annihilation of photons with energy 511 kEv. A type OSGI-A source of photon emission is suitable for the reference source (registration number in the Federal Informational Fund for the Provision of the Units of Measurement (FIFOEI) 58304-14) with the radionuclide ^{22}Na (quantum yield of positrons 90.30% [8]), verified as the first-order working reference.

In the manufacture of loads from a ^{68}Ga solution in the form of hermetically-sealed disks from filter paper, sealed by adhesive tape, identical in form to OSGI-A sources, a wide spacing of the values of ^{68}Ga activity is observed (standard deviation greater than 15%). The scatter of the values of ^{68}Ga activity in the loads may be caused by sorption of multiply charged ions of Gallium on the flask walls. Similar effects were observed in highly effective fluid-flow chromatography [9]. For this reason, the calibration of the reference dose calibrator by the featured method was not conducted.

TABLE 1. The Uncertainty Budget for Calibration by means of a UÉA-7 Installation

Source of uncertainty	Type of estimation	$u(x_i)$, %
Counting rate:		
Pulses from the load	A	0.01
Background pulses	A	0.01
Sensitivity of UÉA-7 installation	B	0.7
Mass of aliquot and solution in flask	B	0.12
Half-life of ^{68}Ga [1]	B	0.36
u_c		0.8
U_p (k = 2)		1.6

Calibration using a gamma-ray spectrometer and ^{18}F. A sample of a hermetically sealed flask of volume 10 mL with a solution of the eluate of ^{68}Ga (hereinafter, the sample) was used for measurements. A sample of a solution of ^{18}F (quantum yield of positrons of 96.86% [10]) in an identical flask was used as the reference source .

The activity of the reference source ^{18}F was measured by the RIS-3A reference dose calibrator, with the calibration coefficient for ^{18}F determined at the VNIIM of D. I. Mendeleyev by means of installations from the formulation of GET 6-2016. The measurement capabilities of the VNIIM of D. I. Mendeleyev were confirmed by involvement in key international comparisons of BIPM. RI (II) - K1.F-18 [11].

The MULTIRAD gamma spectrometer system (registration number in FIFOEI, 68925-17) was used as the comparator. A sample of ^{68}Ga and the reference source ^{18}F were sequentially placed in the same positions at distances of 2 and 3 m from the detection unit of a spectrometer system in order to optimize its frequency load and minimize the differences in the geometry of measurements. In order to ensure complete annihilation of the positrons at the location of emission, samples were placed in a steel container with wall thickness 3 mm.

The time of all measurements was recorded by a timer synchronized with the VNIIFTRI time server. The time of the set of the spectrum was established as no less than 60 s and recorded with a precision of 1 s, which ensured the contribution of standard uncertainty originating due to toradionuclide decay during measurement, no more than 0.2%.

The activity of a sample of ^{68}Ga was calculated for each distance to the detection unit using the following formula:

$$A_{\mathrm{Ga68}} = A_{\mathrm{F18}} \exp\left(-\lambda_{\mathrm{F18}} t_1\right) \frac{\lambda_{\mathrm{Ga68}} t_{\mathrm{Ga68}}}{1 - \exp\left(\lambda_{\mathrm{Ga68}} t_{\mathrm{Ga68}}\right)} \frac{\lambda_{\mathrm{F18}} t_{\mathrm{F18}}}{1 - \exp\left(\lambda_{\mathrm{F18}} t_{\mathrm{F18}}\right)} \frac{s_{\mathrm{Ga68}} \eta_{\mathrm{F18}}}{s_{\mathrm{F18}} \eta_{\mathrm{Ga68}}},$$

where A_{F18} is the activity of the reference source ^{18}F, measured by dose calibrator RIS-3A; λ_{Ga68} and λ_{F18} are the decay constants for ^{68}Ga and ^{18}F, respectively; t_1 is time passed from the moment of the measurement of the activity of the reference source ^{18}F by the RIS-3A dose calibrator until the moment of the beginning of the set of the spectrum of photon emission by ^{18}F; t_{Ga68} and t_{F18} are the time of the set of the spectrum of photon emission of radionuclides ^{68}Ga and 18F, respectively; s_{Ga68} and s_{F18} are the counting rate of pulses at the peaks of total absorption of 511 kEv photons in the spectra of ^{68}Ga and 18F, respectively; and η_{Ga68} and η_{F18} are the quantum yields of photons with energy 511 kEv emitted by radionuclides ^{68}Ga and ^{18}F, respectively.

The calibration coefficient of the dose calibrator was calculated from the values of A_{Ga68} , taking into account the half-life, by the formula

$$K = A_{\mathrm{Ga68}} / (I - I_{\Phi}),$$

where I is the current of the ionization chamber created by the sample with ^{68}Ga, and I_{Φ} is the background current of the ionization chamber.

The value of the calibration coefficient of ^{68}Ga is taken as equal to 1.41, which is the mean value from the results obtained for the distance r = 2 or 3 m to the detection unit of the spectrometer system. Table 2 shows the measurement results of the activity of ^{68}Ga.

TABLE 2. Activity of ^{68}Ga for A_{F18} = 451 MBq

r, m	A_{Ga68}, MBq	K
2	741	1.44
3	595	1.37

TABLE 3. Uncertainty budget (type B) for Calibration using a Gamma-Spectrometer and ^{18}F

Source of uncertainty	$u(x_i)$, %
Activity of the reference source ^{18}F	1.2
Time for accumulation of ^{18}F and ^{68}Ga spectra	0.3
Quantum yield of photons with energy 511 kEv for ^{18}F [10]	0.2
Quantum yield of photons with energy 511 kEv for ^{68}Ga [1]	0.5
Half-lives of ^{18}F [10] and ^{68}Ga [1]	<0.05
Counting rate at the peak of total absorption, ^{18}F and ^{68}Ga	<0.05
Measurement of current	0.2
u_c	1.3
U_p (k = 2)	2.6

TABLE 4. Results of measuring the activity of ^{68}Ga

Method of calibration	A_{Ga68}, MBk	U_p (k = 2)
Calibration with direct traceability to GET 6-2016 (direct method)	75.2	1.6
Calibration using a gamma spectrometer and ^{18}F (indirect method)	74.0	2.6

The uncertainty of the measurements of the activity of a ^{68}Ga sample and the uncertainty of measurements of the current in the ionization chamber make the primary contribution to the total uncertainty of the calibration coefficients. Contributions to the uncertainties of the half-life of ^{68}Ga and of time measurements are negligibly small.

The uncertainty of measurements of current is determined by the nonlinearity of the analog-to-digital converters in the electrometer of the RIS-3A radiometer with the range of the measured activities of a sample of ^{68}Ga and the reference source ^{18}F. In order to determinate the nonlinearity, the dependence of the current of the ionization chamber for decay of ^{18}F by time was measured and compared with the equation for radioactive decay. The nonlinearity is defined as the maximum deviation of measurement results from the calculated.

Table 3 shows the uncertainty budget for calibration using a gamma-ray spectrometer and ^{18}F.

Comparison of various methods of calibration. In order to compare the calibration coefficients of the RIS-3A reference dose calibrator that were obtained by various methods, a 10-mL flask containing a solution of ^{68}Ga was used. Table 4 presents the measurement results of the activity of a radionuclide in the flask with the corresponding uncertainties.

The convergence of measurement results is defined by the formula

$$E = \left|A_{DM} - A_{IM}\right| \Big/ \sqrt{U_{A_{DM}}^2 + U_{A_{IM}}^2}$$

where A_{DM} and U_{DM} are the activity of the ^{68}Ga solution, measured with the calibration coefficient derived by the direct method, and the expanded uncertainty (k = 2), respectively; A_{IM} and U_{IM} are the activity of the ^{68}Ga solution, measured with the calibration coefficient derived by the indirect method, and the expanded uncertainty (k = 2), respectively.

The value of criterion E is 0.53 < 1, which provides evidence of the good convergence of the measurement results of the activity of ^{68}Ga and the applicability of various methods of calibration.

Conclusion. A description of various methods of calibrating the RIS-3A reference dose calibrator on ^{68}Ga activity is presented. A comparison of measurement results of ^{68}Ga activity on the reference dose calibrator with calibration coefficients obtained by different methods was conducted. The possibility of calibrating reference dose calibrators on ^{68}Ga activity using a gamma-ray spectrometer and ^{18}F was confirmed. The results of the study may find application in the calibration of dose calibrators by the activity of other radionuclides with short half-life.

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