Determination of correlated uncertainties of sestamibi- ^{99m}Tc marking

CHS Sousa [1,2], A Gama[3], TGN Camilo[3], CT Mesquita[3], GJ Teixeira[2], JGP Peixoto[1,2]

[1] Universidade do Estado do Rio de Janeiro – UERJ
[2] Instituto de Radioproteção e Dosimentria – IRD/CNEN
[3] Hospital Universitário Antonio Pedro - HUAP/UFF

E-mail: chenriques2@ird.gov.br

Abstract: The input quantities determination involved in radiopharmaceutical marking used in heart scans allowed to estimate the combined and associated standard uncertainty with the process. The *U* value demonstrated that any parameter of the quality control process can be compared and correlated to obtain a real value and validation method, indicating or not, the adequacy of institutional practices and reinforcing the importance of the uncertainties associated to the results in medicine.

Keywords: metrology, ionization chamber, activimeter, uncertainties.

1. INTRODUCTION

Nuclear medicine is a medical procedure that uses labeled molecules with radionuclides, commonly called radiopharmaceuticals, for diagnostic and therapeutic procedures with different objectives. The products quality is important for the diagnostic images accuracy and needs to be controlled [1]. Approximately 95% of all nuclear medicine procedures diagnostic use sodium pertecnetate ($^{99m}TcO_4^-$) obtained from molybdenum-99 (^{99}Mo) generator elution as marker molecules.

The nuclear medicine diagnostic success is a complex process, which relies on the quality procedures, such as radiopharmaceuticals labeling efficiency and accuracy response in measurement and imaging instrumentation. According with technical recommendations [2], all instrumentation used in medicine must pass for periodically performance tests where results will note the operating conditions tools, resulting in unnecessary exposure to ionizing radiation reduction, thereby reducing the radiobiological interactions [3]. The acceptance of the results should be compared to standards values that quantify the variation percentage in relation to the reference values. [4].

It is very often the presentation of measurement results with no metrological parameters such as traceability, or the associated uncertainties determination. The lack of these qualities can compromise any conclusions based on the obtained results [5]. The quantity value determination is never exact, and is therefore necessary to address the uncertainty on the value obtained, which is a result associated parameter and characterizes the values dispersion, making it possible to display separately from independent input quantities and confronting them with the experimental results.

This study aimed to determine the associated uncertainties of the radiopharmaceutical sestamibi-^{99m}Tc marking procedure [6] used in cardiac scintigraphy, correlating it with the quality control of measurement and imaging instrumentation results.

2. MATERIALS AND METHODS

2.1 Materials

Was used a one detector SPECT scintillation camera and a 3.16 cm^3 sensitive volume ionization chamber activimeter. The pharmaceutical drug, sestamibi and technetium-99m used in your markup, were provided by the Instituto de Pesquisas Energéticas e Nuclearers (IPEN).

A flat cobalt-57 source and a vial barium-133 source were used to instrumentation tests, both traceable to Institute of Standards and National. Technology (NIST) with nominal activity 1,3E-2 and 1.8E-5 Ci, respectively. The refrigerator temperature was checked by a digital thermometer with 0.01^{o}C sensitivity.

The radionuclide purity test used a 6.0 mm lead thickness cylindrical container and the remaining tests were used filter paper, chromatographic bowls, specific solvents and universal pH paper.

2.2 Methods

The eluate radiochemical and radionuclide qualities were tested according to standard recommendations on RDC 38 (1), using as samples, aliquots of first generator elution with a 1,0E0 Ci nominal activity.

The radionuclide purity is the ratio expressed in percentage of the radionuclide activity in relation to the total radiopharmaceutical activity. It was verified by the attenuation method, which were measured the activity of the samples and background radiation, adjusting the activimeter for ^{99m}Tc channel, and then for ^{99}Mo channel. The measurements were performed with samples inside the lead cylinder used as ^{99}Mo half value layer. [6]. Thus, it is possible to determine the solution purity (molybdenum break through), and compare it with the recommended limits of 0.15 µCi/mCi (1).

$$MTB = \frac{A_{lig} \; (^{99}Mo)}{A_{lig} \; (^{99m}Tc)}$$

The determination process for chemical purity, which determined the molecule mass percentage of the interest compound on its chemical state shown in relation to the total preparation mass [6] used the semi-quantitative colorimetric method, visually evaluating the results of aluminum concentration.

The activity percentage of target radionuclide in relation to the total activity of the radiopharmaceutical preparation, called radiochemical purity [6] used the thin layer chromatographic method, with stationary and mobile phase. After the chromatographic run, the activity was determined in activimeter, and the results expressed as a function of the reference factor (2).

$$R_f = \frac{distance \; travelded \; by \; the \; radioactive}{distance \; travelded \; by \; the \; solvent}$$

The potential hydrogen (pH) was determined by visual examination by color of the universal paper.

The activimeter precision test for quality results was determined calculating the percentage difference between individual measurements activities [2,4], A_i, and the measurements average, $\bar{A}$, considering a maximum percentage of $\pm$ 5% with 95% of confidence level and correlation between the measured values (3).

$$P = \frac{A_i - \bar{A}}{\bar{A}} \; x \; 100\%$$

The activimeter accuracy test measure the percentage between the average activity measurements, A_i, and the activity of standard reference source, A_v, correcting the radioactive source decay for the measurement day. The results considered a maximum of $\pm$ 10% percent, with a confidence of 90% [2,4], showing the degree correlation between the measured value and the true conventional value (4).

$$A = \frac{1 - A_i}{A_v} \; x \; 100\,\%$$

Was used as quantitative parameters for gamma camera image uniformity evaluating, integral and differential uniformity test, which is considered as interest area, the central field of view, equal to 75% of full image area [8]. The variation of counts accumulated between two pixels of the image, determined the integral percentage (5),

$$U_i = \frac{pixel_{max} - pixel_{min}}{pixel_{max} + pixel_{min}} \; x \; 100\%$$

and the maximum variation between any 5 pixels in any axis determined the differential, given by equation (6).

$$U_d = \frac{pixel_{high} - pixel_{low}}{pixel_{high} - pixel_{low}} \; x \; 100\%$$

The type A uncertainties, considered the standard deviation percentage of the accuracy test series measurements, and type B uncertainties, all other contributions that were not considered repeatability [9].

To the linear correlation between the input quantities x_i and y_i was used the Pearson coefficient (R), where x_i corresponds to independent readings performed measurement, x their arithmetic mean, y_i independent readings sestamibi the labeling efficiency and y the arithmetic mean (6).

$$r_{xy} = \frac{\left(\left(\sum_{i=1}^{n} x_i y_i \right) - \left(\left(\sum_{i=1}^{n} x_i \right) \left(\sum_{i=1}^{n} y_i \right) \middle/ n \right) \right)}{\sqrt{\sum_{i=1}^{n} \left(x_i - \bar{x} \right)^2 \sum_{i=1}^{n} \left(y_i - \bar{y} \right)^2}}$$

Once R is defined, the correlation was analyzed

(Table 2), and the covariance associated was determined with the x_i and y_i input quantities, which are then type A (7).

$$S(\bar{x}, \bar{y}) = \left(\frac{1}{n(n-1)} \right) \sum_{i=1}^{n} (x_i - \bar{x})(y_i - \bar{y})$$

3. RESULTS

The refrigerator temperature presented a 0.6 °C variation, the measure instrumentation don´t show the sensitivity to determine any variation on stabilized electrical network. The automatic zero was checked and adjusted before the measurement series.

The percentage ratios of the radionuclide qualities, radiochemical, labeling efficiency and pH were calculated considering measurements series as normal distributions, and measuring instruments and image quality control testing as rectangular distributions. The combined and expanded standard uncertainties conditions were determined for U (Table 1).

Table 1: The estimation considered uncertainty Type A as obtained by statistical calculation and Type B all of others, as manufacturer information or not calculated results.

Input quantities	Type A (%)	n	Type B (%)
volume			0,0306
radionuclide purity			0,0004
chemical purity			0,0004
uniformity GC			1,1466
standard source			1,7321
accuracy	1,0210	10	1,7321
precision			0,0387
background radiation			0,0024
temperature			0,0006
pH			0,0041
$u =$		3,0528	
$U =$		6,1163	
$k =$		2,00	

The correlation coefficient between independent input quantities accuracy and labeling efficiency showed a weakly positive correlation equal to

0.00002 and covariance equal to 0.450.

Parameter	% results
accuracy	$2,015 \pm 1,00$
efiiciency	$2,35 \pm 0,84$
r	$0,00002$
$s(\bar{x}, \bar{y})$	$0,455$

5. CONCLUSION

The associated uncertainty determination to the sestamibi-99mTc marking process was equal to 6.11% which shows a dependency on extrinsic factors, which if not controlled, can prejudice the outcome of the diagnostic procedure.

The correlation coefficient between the two independent quantities, accuracy and labeling efficiency, showed a weakly positive correlation, showing little linear relationship, however, all parameters must be controlled so that the results remain within the limits of tolerance for the same conditions U.

This paper concludes by suggesting a correlation between the sestamibi99mTc marking process and the images obtained from them, considering the physician perception as a paradigm to be faced by metrology and medicine.

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