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Data reconciliation connected to guard bands to set specification limits related to risk assessment for radiopharmaceutical activity

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ABSTRACT

Radiopharmaceuticals have been used to diagnose several diseases, particularly because the procedure is non-invasive. However, it is important that the correct amount of radiopharmaceutical is used to avoid inaccurate diagnostic results and suboptimal therapeutic outcomes. The amount of the radiopharmaceutical is measured when produced (by the supplier) and a second time (by the receiver), before it's use. When measured at the receiver, the result is corrected for its normal radioactivity decay. Even then, it is possible that both measurements should be considered nominal different or even statistically different when compared through various statistical tools. This research combines two innovative techniques in the field of clinical metrology. The first technique is data reconciliation, which not only enhances measurement accuracy but also reduces measurement uncertainty. The second technique involves using uncertainty information to establish specification limits for compliance assessments. In this way, our proposal aimed to minimize the risk of making incorrect decisions regarding the conformity of the concentration of radiopharmaceutical activity, that is, rejecting an item or batch that is within specification or accepting an item or batch that is outside of specification. A spreadsheet, based on these metrology fundamentals, is available to help the user with the calculations, presenting numerical and graphical results for some common radioisotopes. Reliable specification limits can be calculated and used to determine if the radiopharmaceutical is in accordance with its proposed application.

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1. Introduction

Radiopharmaceuticals are an important resource in the medicine for both diagnostic and therapeutic purposes. Radiopharmaceuticals are used to diagnose and treat diseases, including cancer [1–4]. Radiopharmaceuticals are prepared to target specific organs, tissues, or cells, which allows for more accurate diagnosis and/or treatment. In nuclear medicine, the radiopharmaceuticals are used to produce images of organs or tissues of interest, a process called scintigraphy [5–7], allowing to investigate any abnormalities, which turns the technique in a non-invasive procedure. Furthermore, as the substance containing the radiopharmaceutical is designed to target specific organs, tissues, or cells, the technique increases the effectiveness of treatment while minimizing damage to healthy tissue [8–10]. It is worth noting that the constant improvement of the technique focused on the biological processes encourages the development of new drugs [11–15].

Radiopharmaceuticals are produced through a multi-step process that involves the production of the radioactive substance, synthesis of the non-radioactive compound, and reaction of the radionuclide with the non-radioactive compound [16–18]. The radioactive substance can be produced by irradiating a specific target inside a nuclear research reactor [19,20] or in particle accelerators, such as cyclotrons [21–25]. Once produced, the radioisotopes are tagged onto certain molecules based on biological characteristics, which results in radiopharmaceuticals [26,27]. Because of the risks involved, it is important to know the exact amount of radiopharmaceutical to be intake as it can lead to inaccurate diagnostic results and suboptimal therapeutic outcomes [28,29]. In a routine procedure at a nuclear medicine facility, the Well Type Ionization Chamber is commonly used to measure the concentration of a radiopharmaceutical [30,31]. This measurement result is sent to the receiver together with the radiopharmaceutical. Before being used, the receiver measures the activity once more and corrects its value to the elapsed time between the supplier and the receiver measurements.

Since it is a procedure that involves measurements and their associated decision limits, the development of techniques and applications of various statistical tools has been used by several authors to minimize the errors that may eventually occur [32–38].

Two techniques not yet applied to clinical metrology, when connected, may have great potential to set specification limits related to risk assessment of the activity of radionuclides: data reconciliation (DR) and the use of uncertainty information in the compliance assessment. DR is a technique used to correct measurement errors that are due to measurement noise, i.e., random errors. It is a process of adjusting data derived from two different sources to remove or reduce the impact of the differences identified in the measurements. This technique has been applied in various other fields of study [39–42]. On the other hand, the guard band concept is a technique used to protect against incorrect compliance decisions caused by measurement uncertainty or dispersion. Compliance with the specification is indicated if the result of a measurement is in the region of acceptable values delimited by the guard bands. The use of this technique is also presented with irrelevant numbers in clinical metrology, although with several applicability in other areas, such as [43–48].

This study aims to propose a modified optimization technique based on DR connected to the guard bands concept to set specification limits related to risk assessment of the radiopharmaceutical activity.

2. Methodology

The methodology used herein was divided into three parts: (i) obtaining and correcting activity concentration values over time for some radiopharmaceuticals; (ii) application of DR technique; and (iii) use of the uncertainty information for the risk assessment.

2.1. Experimental procedure

Activity concentration data of some radiopharmaceuticals from a nuclear medicine facility were utilized herein. The equipment employed to measure the activity concentration was a commercially available radionuclide calibrator. This calibrator comprises a well-type air ionization chamber and an electrometer. The radiopharmaceuticals used were Ga-67, I-131, I-123, Lu-177, Ra-223 and Tc-99 m, Table 1.

To enable the application of DR and, posteriorly, to apply uncertainty information in compliance assessment, the first step was to correct in time the activity concentrations obtained from both the manufacturer and the nuclear medicine facility. This was necessary because the predicted activity of the radiopharmaceutical provided by the supplier is for a specific time, which may not necessarily align with the time of measurement conducted at the nuclear medicine facility. The intake of the radiopharmaceutical can occur before or after the predicted time, based on the facility's demand. Therefore, a schedule of activity measurements was compiled, and the

Table 1
Radiopharmaceuticals and their respective uses in nuclear medicine facility.

Radiopharmaceutical	Half-life (minutes)	Use
Ga-67	4696.848	Diagnose of certain types of cancer, such as Hodgkin's disease, lymphoma, or lung cancer; and acute swollen lesions [49].
I-123	793.38	In gamma scintigraphy as a tracer and more specifically to localize thyroid carcinoma metastases [50].
I-131	11556.288	Treatment of some diseases and cancer of the thyroid gland; and diagnosis of liver and kidney function [51].
Lu-177	9567.792	Treatment of adults with a type of cancer known as gastroenteropancreatic neuroendocrine tumors [52].
Ra-223	16459.2	Internal radiation therapy treatment for advanced prostate cancer that has spread to the bones [53].
Tc-99 m	360.432	Medical diagnostic imaging scans along all parts of the body [54].

values were time-corrected. Subsequently, DR was applied, followed by the uncertainty information in compliance assessment.

2.2. Data reconciliation (DR)

DR uses measurement redundancies to minimize the measurement uncertainties and reduce the random errors. This technique is based on laws of conservation and process constraints. Two or more experimental values, m^e, can be reconciled to a single reconciled value, m^c that best represents them all [55].

The statistics, involved in this approach, considers that data is subject to fluctuations modelling by a multivariate normal, considering that there are no systematic errors, the model is perfect, and the errors follow a Gaussian distribution. Based on these assumptions, the DR probability density function, considering the V as the variance-covariance matrix, can be defined by Eq. (1):

$$P(X) = \frac{1}{\left((2\pi det V)^N\right)^{1/2}} exp\left[-\frac{1}{2}(m^e - m^c)^T V^{-1}(m^e - m^c)\right] \tag{1}$$

Therefore, a schedule of activity measurements was compiled, and the values were time-corrected. Subsequently, DR was applied, followed by the uncertainty information in compliance assessment.

Here, one uses the measurement uncertainty, U, as a parameter to express the variabilities (V matrix), considering N points of equal probability density in the region of maximum reliability. For example, U_{11}^2 considers the covariance between m_1^e and m_1^c.

$$m^e = \begin{bmatrix} m_1^e \\ m_2^e \\ \vdots \\ m_N^e \end{bmatrix} \quad m^c = \begin{bmatrix} m_1^c \\ m_2^c \\ \vdots \\ m_N^c \end{bmatrix} \quad V = \begin{bmatrix} U_{11}^2 & U_{12}^2 & \cdots & U_{1N}^2 \\ U_{21}^2 & U_{22}^2 & \cdots & U_{2N}^2 \\ U_{i1}^2 & U_{i2}^2 & \cdots & U_{iN}^2 \\ \vdots & \vdots & \ddots & \vdots \\ U_{N1}^2 & U_{N2}^2 & \cdots & U_{NN}^2 \end{bmatrix}$$

After optimizing the objective function considering the quantities are not correlated, and following the steps proposed by Ref. [39], the reconciled value and its reconciled expanded uncertainty can be calculated, based on Bayesian Statistics [56], respectively, by Eqs. (2) and (3):

$$m^c = \frac{\frac{m_1^e}{U_{11}^2} + \frac{m_2^e}{U_{22}^2} + \cdots \frac{m_N^e}{U_{NN}^2}}{\frac{1}{U_{11}^2} + \frac{1}{U_{22}^2} + \cdots + \frac{1}{U_{NN}^2}} = \frac{\sum \frac{m_i^e}{U_i^2}}{\sum \frac{1}{U_i^2}} \tag{2}$$

$$U_{m^c} = \sqrt{\frac{1}{\sum \frac{1}{U_i^2}}} \tag{3}$$

Here, since these previous parameters depend solely upon the supplier and receiver values, and their respectively uncertainties, Eqs. (2) and (3) are simplified to Eqs. (4) and (5), respectively:

$$\mathbf{m^c} = \frac{\sum \frac{\mathbf{m_i^e}}{\mathbf{U_i^2}}}{\sum \frac{\mathbf{1}}{\mathbf{U_i^2}}} = \frac{\frac{\mathbf{m^e_{supplier}}}{\mathbf{U^2_{supplier}}} + \frac{\mathbf{m^e_{receiver}}}{\mathbf{U^2_{receiver}}}}{\frac{\mathbf{1}}{\mathbf{U^2_{supplier}}} + \frac{\mathbf{1}}{\mathbf{U^2_{receiver}}}} \tag{4}$$

$$\mathbf{U_{m^c}} = \sqrt{\frac{\mathbf{1}}{\sum \frac{\mathbf{1}}{\mathbf{U_i^2}}}} = \sqrt{\frac{\mathbf{1}}{\frac{\mathbf{1}}{\mathbf{U^2_{supllier}}} + \frac{\mathbf{1}}{\mathbf{U^2_{receiver}}}}} \tag{5}$$

2.3. Use of the uncertainty information in compliance assessment

Measurement uncertainty has been used in several metrological areas related to medical tests such as quality control [57–60], traceability and harmonization [61] and validation studies [62]. On the other hand, this work found a gap in radiopharmaceuticals regarding the use of uncertainty information as a powerful tool to assess if a result meets the specification, in contrast to other sciences.

By taking measurement uncertainty into account, risks to the producer (rejecting an item within specification) and risks to the consumer (accepting an item outside specification) can be minimized. Such risks can be classified as global when they refer to an untested item or specific risks, related to a tested item [63].

This tool has been incorporated into different areas of knowledge such as oil and gas industry [42,64], environmental protection [65], the security of process [66], compliance assessment in nuclear medicine facilities [47] and risk assessment in monitoring of water analysis [67].

However, doubtful risk assessments may arise when partial overlaps between measurement uncertainties and upper and lower specification limits are noted, Fig. 1.

Fig. 1 shows the acceptance zone, constructed by reducing the tolerance interval on both sides by guard bands, g (within dashed

lines), intervals between tolerance limits, defined by upper and lower specification limits (USL and LSL, respectively), and corresponding acceptance limits. Considering exactly a 5 % significance level, each guard band is calculated by multiplying the standard uncertainty, u, by 1.64 [68]. The acceptance interval can be expressed by USL minus 1.64 u and LSL plus 1.64 u, focusing on the probability of false acceptance risk (consumer risk or Type II error). On the other hand, the acceptance interval can be expressed by USL plus 1.64 u and LSL minus 1.64 u, focusing on the probability of false rejection risk (producer risk or Type I error). Finally, when considering a shared risk, the width of the guard band is zero (L = 0), that is, suppliers and recipients equally share the risks of false decisions, 50 % for each [63].

Using the Monte Carlo method (MCM), 50,000 simulated values were generated for each input data that are available in an MS-Excel spreadsheet in supplementary material. Based on this information, histograms are built out by 50,000 pseudorandom values for each radionuclide and its associate parameters, using the MS-Excel function " = NORM.INV(RANDON(); y_i; X_{y_i})", where y_i is the measured value and X_{y_i} is the standard uncertainty for the i^{th} parameter). Next, the total global consumer risks were calculated as the ratio between the number of simulated values outside the tolerance limits and the total number of simulated values [69]. The main aim of this spreadsheet is to calculate reliable specification limits to determine if the radiopharmaceutical is in accordance with its proposed application.

Taking advantage of redundant measurements corrected by supplier and receiver time, the aim of this study was to connect the concept of DR and guard band to define specification limits related to the risk assessment of radionuclide activity.

3. Results and discussion

After data processing, an Excel spreadsheet was provided with this manuscript as Supplementary Material to manually establish the lower and upper specification limits such that the consumer risk of the reconciled value, complies with the specification. The editable cells are on a blue-sky background and must be filled, such as radionuclide, difference between supplier and receiver measurement time, expanded uncertainty (or standard uncertainty for k = 1) and its respective coverage factor and guard band choice. Finally, cells C8 and E8, in yellow, are also editable and must be the last ones to be filled in, as they are the output quantities, that is, lower and upper specification limits. This completion is by trial and error and depends on two parameters: (i) its average value must be the same as in cell C32 and (ii) observe the desirable risk value (as close as possible to 5 %, without exceeding it) in cell F47. When measurement uncertainty is very high, the acceptance range can be very narrow (even non-existent).

As the uncertainty for each radiopharmaceutical was expressed as typical standard uncertainty, the coverage factor (k) to be used in the spreadsheet is 1.

The last cells to the filled are the "Lower Specification Limit" and the "Upper Specification Limit". The media of these two parameters must be the same of the "Corrected value" of the "Receiver's measurement" and based on trials, these parameters must be filled until the "Risk value" of the "Reconciled measurement" is the closest value equal to or less than 5 %, significance level for the risk assessment.

Although the International System of Units for radioactivity considers Becquerel, this study used Curie because it is commonly used in nuclear medicine facilities (1 Ci corresponds to 3.7·1010 Bq).

3.1. Obtaining the significance level

For Ga-67, the supplier and receiver measurements were 10 mCi and 11.1 mCi (no correction in time), respectively, considering a

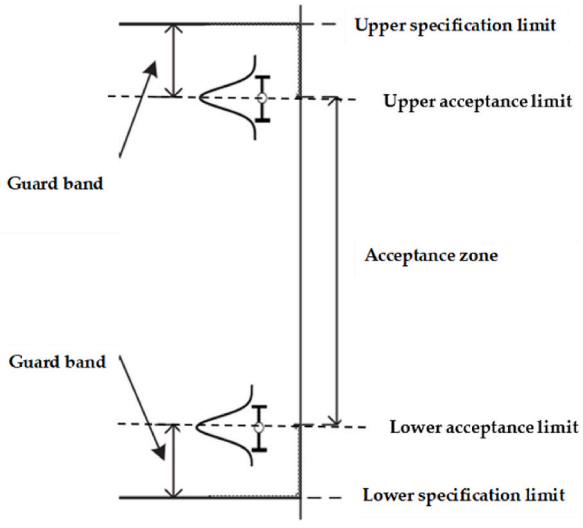

Fig. 1. Upper and lower limits for the consumer risk.

time difference between them of 371 min and a typical standard uncertainty (k = 1) of 15.0 % [70]. Based on the connected approaches of DR and guard band, the consumer risk for the supplier, receiver and reconciled measurements were, respectively, 14.5 % (not conforming to the specification), 9.15 % (not conforming to the specification) and 4.59 % (10.19 mCi–10.82 mCi, considering a standard deviation, conforming to the specification), generating reliable specification limits of 8.41 mCi–12.6 mCi, Fig. 2.

For I-123, the supplier and receiver measurements were 5.13 mCi and 5.13 mCi (no correction in time), respectively, considering a time difference between them of 75 min and a typical standard uncertainty (k = 1) of 11.0 % [71]. Based on the connected approaches of DR and guard band, the consumer risk for the supplier, receiver and reconciled measurements were, respectively, 20.8 % (not conforming to the specification), 6.86 % (not conforming to the specification) and 5 % (4.64 mCi–4.96 mCi, considering a standard deviation, conforming to the specification), generating reliable specification limits of 4.01 mCi–5.59 mCi, Fig. 3.

For I-131, the supplier and receiver measurements were 150.0 mCi and 155.1 mCi (no correction in time), respectively, considering a time difference between them of 480 min and a typical standard uncertainty (k = 1) of 14.0 % [72]. Based on the connected approaches of DR and guard band, the consumer risk for the supplier, receiver and reconciled measurements were, respectively, 12.6 % (not conforming to the specification), 12.0 % (not conforming to the specification) and 5 % (150.3 mCi–151.1 mCi, considering a standard deviation, conforming to the specification), generating reliable specification limits of 125.9 mCi–175.5 mCi, Fig. 4.

For Lu-177, the supplier and receiver measurements were 200.0 mCi and 202.0 mCi (no correction in time), respectively, without time difference between them and a typical standard uncertainty (k = 1) of 0.24 % [73]. Based on the connected approaches of DR and guard band, the consumer risk for the supplier, receiver and reconciled measurements were, respectively, 20.2 % (not conforming to the specification), 0.05 % (conforming to the specification) and 4.18 % (201.0 mCi–203.0 mCi, considering a standard deviation, conforming to the specification), generating reliable specification limits of 200.4 mCi–203.6 mCi, Fig. 5.

For Ra-223, the supplier and receiver measurements were 0.178 mCi and 0.160 mCi (no correction in time), respectively, considering a time difference between them of - 283 min and a typical standard uncertainty (k = 1) of 10.0 % [74]. Based on the connected approaches of DR and guard band, the consumer risk for the supplier, receiver and reconciled measurements were, respectively, 25.8 % (not conforming to the specification), 4.82 % (conforming to the specification) and 4.92 % (0.155 mCi–0.169 mCi, considering a standard deviation, conforming to the specification), generating reliable specification limits of 0.135 mCi–0.189 mCi, Fig. 6.

For Tc-99 m, the supplier and receiver measurements were 25.0 mCi and 24.4 mCi (no correction in time), respectively, considering a time difference between them of - 10 min and a typical standard uncertainty (k = 1) of 0.72 % [75]. Based on the connected approaches of DR and guard band, the consumer risk for the supplier, receiver and reconciled measurements were, respectively, 20.2 % (not conforming to the specification), 6.15 % (not conforming to the specification) and 4.64 % (24.8 mCi–24.9 mCi, considering a standard deviation, conforming to the specification), generating reliable specification limits of 24.6 mCi–25.2 mCi, Fig. 7.

Summarising on the risk assessment of the six radiopharmaceuticals: (i) the width of the acceptance interval depends on the magnitude of the standard uncertainty, that is, higher intervals is observed for Ga-167, I-123, I-131 and Ra-223 (uncertainties above 10 %), when compared to Lu-177 and Tc-99 m (uncertainties below 1 %); (ii) the consumer risk for suppliers is so high in all cases, because the suppliers deliver the activity as close as possible to the specification limit and; (iii) the values of the lower and upper specification limits were optimized by the DR routine connected to guard band approach and the experts' view is what determines whether the given radiopharmaceutical is in accordance with the proposed application.

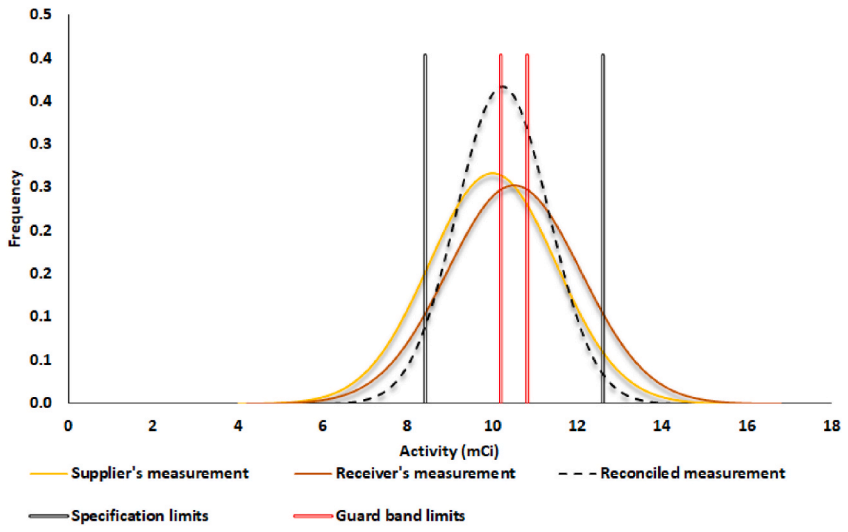

Fig. 2. Histograms for 5 % significance level, Ga-67 activity.

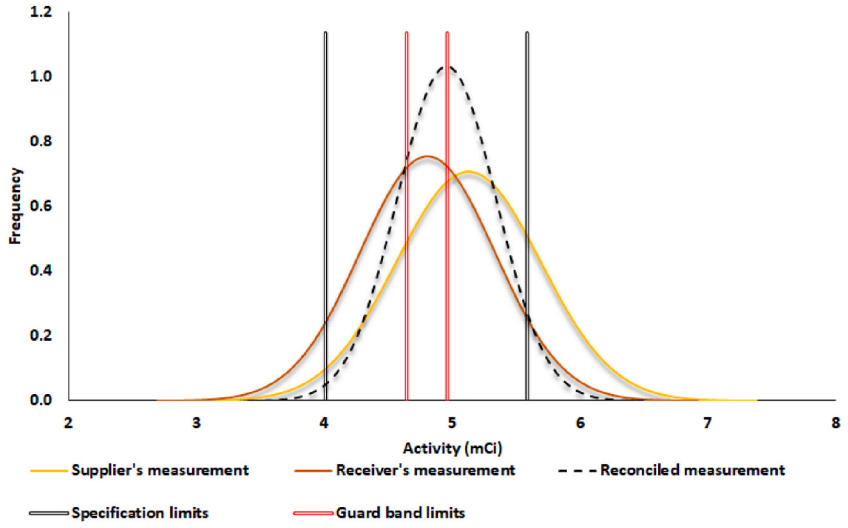

Fig. 3. Histograms for 5 % significance level, I-123 activity.

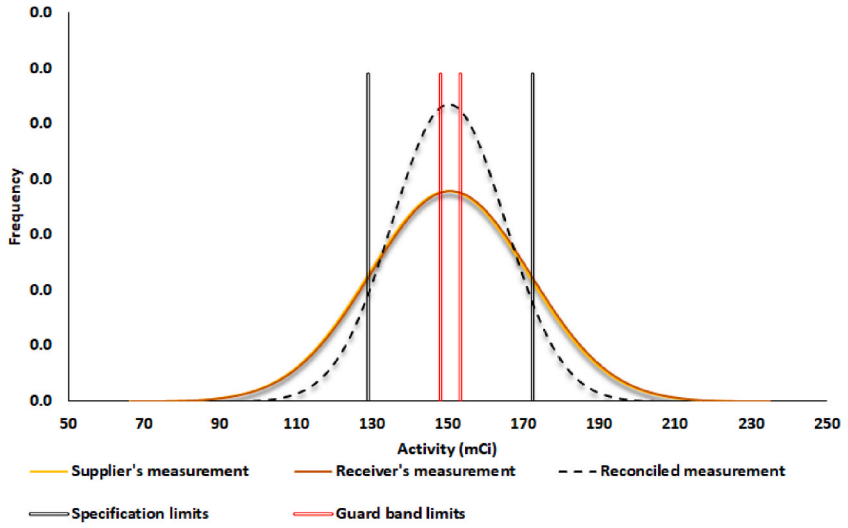

Fig. 4. Histograms for 5 % significance level, I-131 activity.

3.2. Guiding an agreement policy between requesters the supplier

Fig. 8, obtained from the spreadsheet provided as supplementary material, illustrates the behavior of the risk of reconciled measurement as a function of both the receiver's and supplier's measurement uncertainty, ranging from 1 % to 10 % of the mean value [47], for any mean value that is equally determined by both the receiver and the supplier.

When assessing the quality of activity concentration measures by adopting a statistically acceptable value of reconciled measurement risk, it is essential to consider risks below 5 %, as practiced in international standards [68]. It is notably noticeable from Fig. 8 that meeting this condition (risk below 5 %) requires at least one of the calibrators to have measurement uncertainties below 1 % of the mean value (the blue bars were fixed at 1 % uncertainty where risks are below 5 %). Therefore, it is concluded that if both calibrators have, at least, uncertainties of 2 %, the risk of the reconciled measurement increases to approximately 15 %.

Perceive that evaluating this type of behavior is essential because one of the requirements to improve measures in radiopharmacy is to establish policies and procedures for calculating the activity concentration of radiopharmaceutical [35,76]. This tool can be used by both suppliers and nuclear medicine facilities, enabling that an agreement can be reached between the two parties to establish a maximum acceptable risk for the measurements, utilizing this tool as a negotiating device. Likewise, once the acceptable risk criteria are established between the requester and the supplier, the production cost can be directly affected since the supplier will know which limits need to be met.

Similarly, the obtained risk values over time can be catalogued to monitor the quality of the measurement and, consequently, the

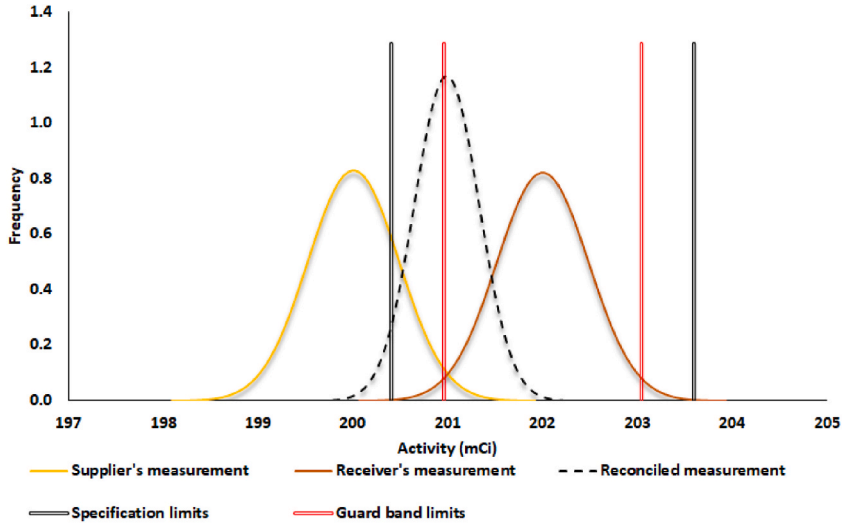

Fig. 5. Histograms for 5 % significance level, Lu-177 activity.

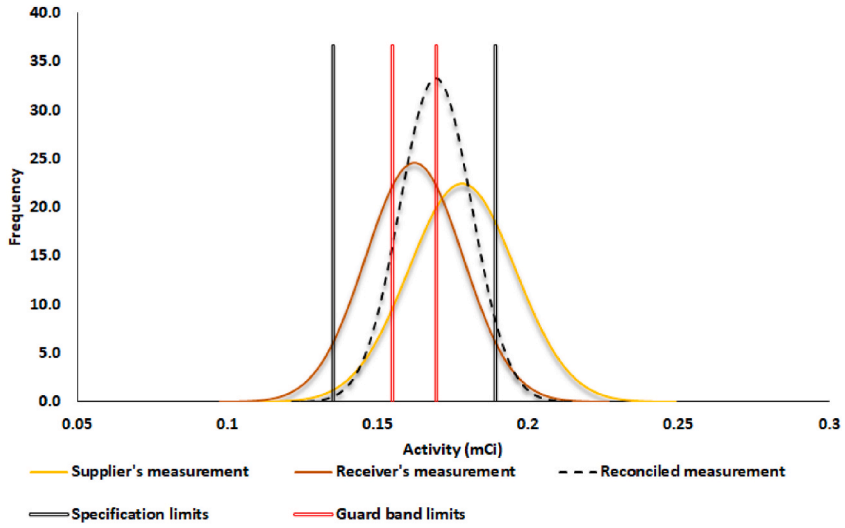

Fig. 6. Histograms for 5 % significance level, Ra-223 activity.

accuracy in the radiopharmaceutical intake, directly impacting in dose accuracy, another crucial criterion for a nuclear medicine facility. It allows for the ALARA principle (As Low As Reasonably Achievable) of radiation safety to be fulfilled. This is important for the medical physicist professional since the catalogue of activity concentration over time can assist in decision-making in a facility.

Although instrument calibration and testing procedures are routine in a nuclear medicine facility, it is crucial for Laboratory Medicine professionals to recognize the importance of specifying the uncertainty associated with the measurement of radiopharmaceutical activity, an aspect that currently may not receive sufficient attention within nuclear medicine facilities.

Finally, it is worth highlighting that the scope of this research does not encompass discussing whether the results obtained for each radiopharmaceutical are in line with their applicability. This is because the activity concentration of the radiopharmaceutical, the amount radiopharmaceutical intake, the chosen radiopharmaceutical, and the location/size of the tumour are all part of an individualized treatment. Therefore, the deemed "acceptable" uncertainty and specification limits will depend on specific patient conditions.

4. Conclusions

The application of both techniques, namely data reconciliation and the use of uncertainty information about the radioisotope, made it to establish an interval, for a significance level of 0.05, in which the true radiopharmaceutical activity is.

The spreadsheet prepared allows the receiver to decide whether the radiopharmaceutical is in accordance with its applicability. Moreover, its use does not imply the knowledge of any of both mathematical techniques by the receiver who, in general, has medical

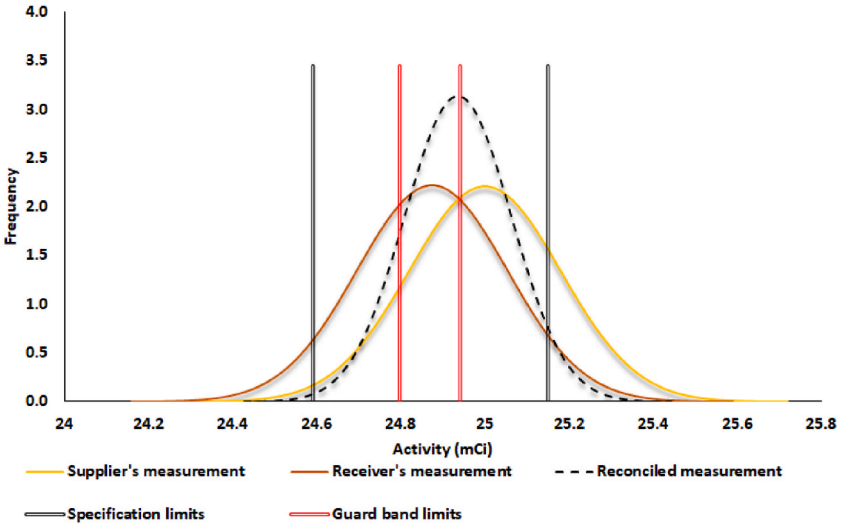

Fig. 7. Histograms for 5 % significance level, Tc-99 m activity.

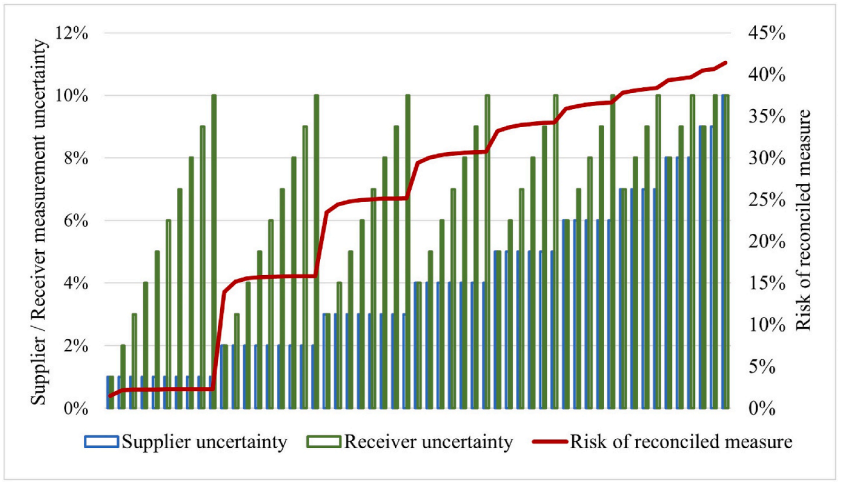

Fig. 8. Behavior of the risk of reconciled measurement as a function of measurement uncertainties.

background.

As future work, the authors suggest evaluating the measurement uncertainty resulting from sampling in addition to the analytical uncertainty to ensure that the variability used in the DR and guard band approaches are not underestimated. Furthermore, medical physics professionals could suggest guidelines for deciding whether a specific radiopharmaceutical meets its applicability based on optimized specification limits calculated by the proposal presented in this study.

Data availability statement

Data used is included in the article.

CRediT authorship contribution statement

Wagner do Prado Pereira: Writing - original draft, Visualization, Data curation. **Luciana Carvalheira:** Writing - review & editing, Writing - original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **José Marques Lopes:** Writing - review & editing, Writing - original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Paula Fernandes de Aguiar:** Writing - review & editing, Writing - original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rosana Medeiros Moreira:** Writing -

original draft, Visualization, Funding acquisition, Data curation. **Elcio Cruz de Oliveira:** Writing - review & editing, Writing - original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22992.

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