

Quality control on radiochemical purity in Technetium-99m radiopharmaceuticals labelling: three years of experience on 2280 procedures

Claudio Maioli^{1,2}, Giovanni Lucignani^{1,2}, Aldo Strinchini², Luca Tagliabue²,
Angelo Del Sole^{1,2}

¹Nuclear Medicine Unit, Department of Health Sciences, University of Milan, Italy; ²Nuclear Medicine Unit, Department of Diagnostic Services, San Paolo Hospital, Milan, Italy

Summary. *Objective:* the purpose of this study was to offer an example of evaluations of the ISO9001 certified internal quality assurance (QA) system of ^{99m}Tc-radiopharmaceutical preparations and quality control in vivo use, using industrial kits and generators in order to identify possible sources of errors in the procedures labeling and quality control procedures. *Methods:* The study was performed at a single institution over a period of three years (July 1st, 2011 - July 1st, 2014), and included a total of 2280 radiopharmaceutical preparations prepared by four different technologists. All the radiopharmaceutical preparations and quality controls were performed according to each SPC provided by the manufacturer. The radiopharmaceutical preparations were the following (trade names are reported in brackets): ^{99m}Tc-albumin colloid [Nanocoll] (n=349), ^{99m}Tc-oxidronate [Technescan[®]hdp] (n=701), ^{99m}Tc-exametazime [Ceretec] (n=169), ^{99m}Tc-sestamibi [Cardiolite] (n=92), ^{99m}Tc-albumin aggregated [Technescan[®]lyomaa] (n=140), ^{99m}Tc-tetrofosmin [Myoview] (n=567), ^{99m}Tc-diethylene triamine pentacetic acid [Technescan[®]dtpa] (n=254), and ^{99m}Tc-dimercapto succinic acid [Renocis[®]] (n=8). Data were analyzed to determine the number and type of radiopharmaceutical labelling failure and to derive the sources of these failures to define corrective actions and optimize the quality assurance program. *Results:* A total of 2280 procedures were performed and recorded. Following the quality control procedure six out of the 2280 preparations (0.26%) were non-conforming for clinical use with the RCP limits indicated in the SPC. Five of these were due to gross technical errors in measurements and manual procedures and were immediately repeated, returning within the limits of acceptability. The sixth failure was due to short incubation time, though compliant with the manufacturer's instructions. *Conclusions:* We concluded that the quality of the final product depends on a controlled production system based on the implementation of specific standard operating procedures (ISO9001, SOP) for each radiopharmaceutical production, according to strict adherence to the SPC of each radiopharmaceutical. Based on these conclusions, in our opinion every quality control suggesting a possible error in the synthesis procedure recommended in the SPC should be immediately reported to the manufacturer, for a revision of the SPC, as well as to the regulatory agencies for an alert. This strategy may in fact allow the continuous improvement of the labelling procedures and therefore the optimization of the quality control procedures frequency to ensure both patients safety and a more rational management of resources for economic sustainability. (www.actabiomedica.it)

Key words: pertechnetate, radiochemical purity testing, radiopharmaceutical, ^{99m}Tc, thin-layer chromatography

Introduction

A radiopharmaceutical is “any medicinal product which, when is ready for use, contains one or more incorporated radionuclides, for medical purposes” (1). From the regulatory point of view, the radiopharmaceutical must be sterile, pyrogen-free, safe and effective. Therefore, quality assurance and radiochemical purity testing (RCP) are considered mandatory steps in the process of radiopharmaceutical synthesis, as well as radio-labelling according to national laws and guidelines in compliance with European directives (2). In the case of radiopharmaceuticals prepared by industrial kits, through radioactive labelling within the unit where they are used, the responsibility for their quality at the time of administration to patients falls under the responsibility of the nuclear medicine specialist and an “on-site labelling process”. In short, using commercial kits and generators requires an “on-site control of the labelling process” (2).

In particular, every preparation consists of manual procedures repeated daily that may be influenced by multiple factors (Table 1) (2), so each preparation should be evaluated for RCP and sterility (4, 5).

The RCP is defined as the ratio between the desired radio-labelled species and the total radioactivity in a sample (4). There is strong evidence that control of routine RCP has resulted in multiple benefits. For example, the RCP has identified a problem in the past in the preparation of ^{99m}Tc -tetrofosmin (Myoview, GE Healthcare) and MAG3 (2). In addition, there are situations in which the RCP is mandatory for each radiopharmaceutical preparation, such as for the use of unlicensed products, investigational medicinal products or validation of extended expiry or deviation from

the manufacturer’s directions (2). Therefore, RCP is a fundamental parameter of QA as specified in the SPC, national law (5) and application of point 7.1 of UNI EN ISO9001 (21).

The preparation and quality control of RCP of radiopharmaceutical is done in routine practice by following the SPC accompanying every kit. Since only a few recent studies are available about the determination of RCP of ^{99m}Tc -labelled radiopharmaceuticals (4, 6, 7), in this study we aimed at corroborating and confirming the results of previous studies. To this end, over a period of three years we assessed the RCP and radiochemical impurities of $^{99m}\text{TcO}_2$ and $^{99m}\text{TcO}_4$, all radiopharmaceutical preparations labelled with ^{99m}Tc . We also tested the influence of a variable represented by the time (72 hours) between two consecutive generator elutions, as this variable may affect RCP (8-10). Finally, we also evaluated the cost related to the daily performance of RCP.

Materials and methods

The RCP of radiopharmaceuticals labelled with ^{99m}Tc was routinely assessed by standard techniques. For determination of RCP we used the recommendations of the European Pharmacopoeia and the manufacturer’s procedures reported in the SPC inserted into the kits (Table 1).

Freeze-dried radiopharmaceuticals were reconstituted with a solution of ^{99m}Tc , eluted by a Generator (Drytec GE Healthcare Limited Amersham Place, United Kingdom) 24 hours after the previous elution. In 291 preparations the ^{99m}Tc solution was eluted 72 hours after the previous one as recommended by man-

Table 1. Methods for the determination of the Radiochemical Purity of ^{99m}Tc radiopharmaceuticals and European Pharmacopoeia limits

Radiopharmaceutical	Method	Reagents	Limits %
^{99m}Tc - albumin colloid	TLC	Methanol-water 85:15 v/v ITLC-SG	>95
^{99m}Tc -oxidronate	TLC	Sodium acetate, Methylethylketone ITLC-SG	≥95
^{99m}Tc -exametazime	TLC	Saline, Methylethylketone ITLC-SG	≥80
^{99m}Tc -sestamibi	TLC	Ethanol/aluminium oxide	≥94
^{99m}Tc -albumin aggregated	Filtration	3 µm filter/saline	≥90
^{99m}Tc -tetrafosmin	TLC	Acetone-Dichloromethane 35:65 v/v ITLC-SG	≥90
^{99m}Tc -diethylene triamine pentaacetic acid	TLC	Saline, Methylethylketone ITLC-SG	≥95
^{99m}Tc -dimercaptosuccinic acid	TLC	Methylethylketone/Whatman	≥95

ufacturers, and the activity used for labelling did not exceed the maximum allowed; the highest permitted reconstruction activity was used in 75% of tetrofosmin preparations (12000 MBq) and in 80% of HDP preparations (7400 MBq). All preparations were carried out by 4 technologists with at least 10 years of experience (11), under the supervision of a nuclear medicine physician and a production manager, following standard radioprotection rules. The quality control of the RCP was performed using ITLC-SG chromatography, TLC (for ^{99m}Tc -sestamibi) or filtration (for ^{99m}Tc -albumin aggregated). Volume measurements of radiopharmaceuticals were taken using a validated precision pipette (RAININ Finpipette, U.S.A.) with a range of dispensation between 7 and 20 μl , while volumes of the solvents for chromatography of analytical grade were dispensed using precision glass pipettes (maximum volume 10 ml). Chromatographic borosilicate trays were used and each radiopharmaceutical was tested in its own chromatography tank. For radioactivity counting, chromatographic paper was cut only at the solvent front: as a result, expansion of the radioactive material on the paper chromatography was avoided, improving the accuracy of the measurement. Measurements of radioactivity for calculation of RCP and radiochemical impurities, ($^{99m}\text{TcO}_2$ and $^{99m}\text{TcO}_4$) were made using the "cut and count" technique and a validated dose calibrator (ACN Isodose, Cerro Maggiore, Milan, Italy), and a validated technique, as previously reported (13). All measurements were carried out taking sufficient time to obtain a C.V. $\leq 5\%$. The counting geometry of the chromatography paper in the dose calibrator was standardized for all quality controls. All quality controls of the RCP were made before the radiopharmaceutical administration to the patient, as well. The storage temperature of pharmaceuticals before labelling was monitored by a computerized system in continuous (T-Guard Biomed Consulting, Como, Italy) and all pharmaceuticals were stored in a temperature range of 2–8°C. In one unforeseeable situation, due to electric energy supply interruption, storage temperature of unlabeled kits reached 22°C for 24 hours; no alterations were observed following the quality control procedure of samples from these kits. Radiopharmaceuticals were prepared and used before the expiration date, under a laminar flow

dedicated hood (Eliza, Comecer, Castel Bolognese, Ravenna, Italy), in accordance with the SPC. The generator to be eluted and radiopharmaceutical lot to be used was chosen by a computer program for laboratory management. The injected activity, the volume of reconstitution and incubation times were controlled directly by the technician staff.

All operating procedures have been described in the handbook for quality assurance developed in the unit and are ISO9001 certified.

Statistical analysis: data were analyzed using an "R" program. Descriptive statistics were calculated and are shown as median, first and third quartile, analysis of variance. The level of statistical significance was set at a *P* value less than 0.05. Comparison of variables was performed using a two-sample Kolmogorov-Smirnov test.

Results

The results of RCP determination and radiochemical impurities of all 2280 preparations are listed in Table 2. The frequency distribution of the RCP is shown in Figures 1 to 7. Six out of 2280 preparations appeared not to meet the quality criteria (0.26%). Two of these (^{99m}Tc -tetrofosmin) were due to a technical failure of the quality control procedure (gross human error due to the exchange of solvents). In a third case concerning the preparation of ^{99m}Tc -albumin colloid the quality control revealed that the manufacturer's instructions on incubation time, 5 to 10 minutes, were incorrect. In our first quality control on this radiopharmaceutical it became evident that this time is insufficient for acceptable RCP in albumin colloid labelling and that 60 minutes may be more appropriate; in the recent SPC the recommended time is actually >30 minutes. All subsequent preparations were incubated for 1 hour.

In cases of ^{99m}Tc -oxidronate and ^{99m}Tc -diethylene triamine pentaacetic acid, there were three failures due to insufficient measurement time because the preparation concerned only one preparation and was approximately 1 MBq. We found that 2 lots of ^{99m}Tc -oxidronate were statistically different from the other lots of ^{99m}Tc -oxidronate ($p=0.04$ with values of RCP

Table 2. Summary of results for Radiochemical Purity and Impurity determinations (n=2280)

Radiopharmaceutical	N° tested	Radiochemical Purity %			$^{99m}\text{TcO}_4^-$ %			$^{99m}\text{TcO}_2$ %			N° of failures
		Range	Median	1q-3q	Range	Median	1q-3q	Range	Median	1q-3q	
^{99m}Tc -albumin colloid	349	89.1-100	98.7	98-100	0-10.9	1.3	0.6-2	-	-	-	1*
^{99m}Tc -oxidronate	701	94.7-100	98.8	98.3-100	0-3.1	0.7	0.3-1.1	0-4.1	0.4	0.1-0.7	1**
^{99m}Tc -exametazime	169	80.5-96.5	90.3	87.8-96.5	0-10	1.8	1.2-2.5	3.1-6 (a)	7.7 (a)	6.2-9.8 (a)	0
^{99m}Tc -sestamibi	92	95-100	97.9	96.8-100	0-5 (b)	2.2 (b)	1.3- 3.3 (b)	-	-	-	0
^{99m}Tc -albumin aggregated	140	91.5-99.8	96.9	95.7-99.8	0.2-8.5 (c)	3.2 (c)	2.5-4.3 (c)	-	-	-	0
^{99m}Tc -tetrafosmin	567	11.3-99.9	97.3	96.7-99.9	0-86.3	0.1	0-0.2	0-5.7	2.5	0-0.2	2**
^{99m}Tc -diethylene triamine pentaacetic acid	254	91.3-100	99.7	98.9-100	0-4.6	0	0-0.4	0- 8.7	0	0-0.6	2**
^{99m}Tc -dimercaptosuccinic acid	8	99.5-100	100	99.9-100	0-0.6	0	0-0.1	-	-	-	0

*failures in kit manufactures's instructions (see Results); **failures in quality control (see Results)

(a) $^{99m}\text{TcO}_2 + ^{99m}\text{Tc II}^{\circ}$ HMPAO; (b) Total radioactivity impurity; (c) Radioactivity passing the membrane

lower than average), although falling within the limits of the European Pharmacopoeia and in any case, this fact cannot be attributed to the internal preparations. All other lots of radiopharmaceuticals had no statistically significant differences ($p=ns$).

Table 3 displays the reported results of RCP and radiochemical impurities of 459 preparations, carried out with ^{99m}Tc eluted 72 hours after the first elution of the generator of ^{99m}Tc (the first elution is discarded in accordance with the NBP). There was no statistical

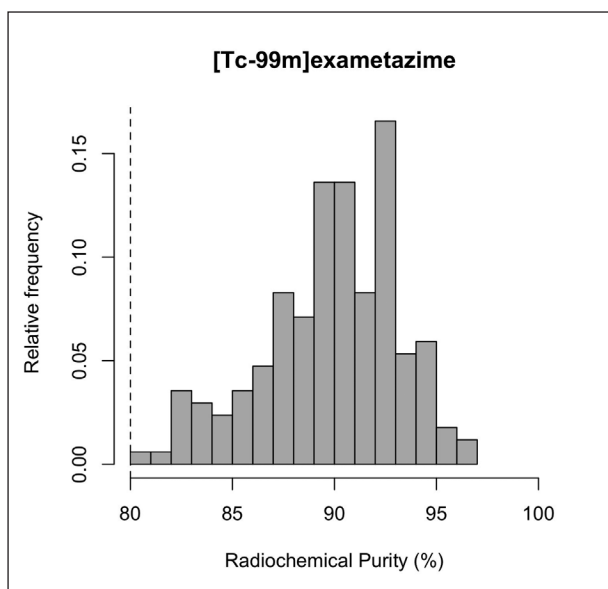


Figure 1. Relative frequency of radiochemical purity of 7 radiopharmaceuticals preparations. The vertical line represents the European Pharmacopoeia limits

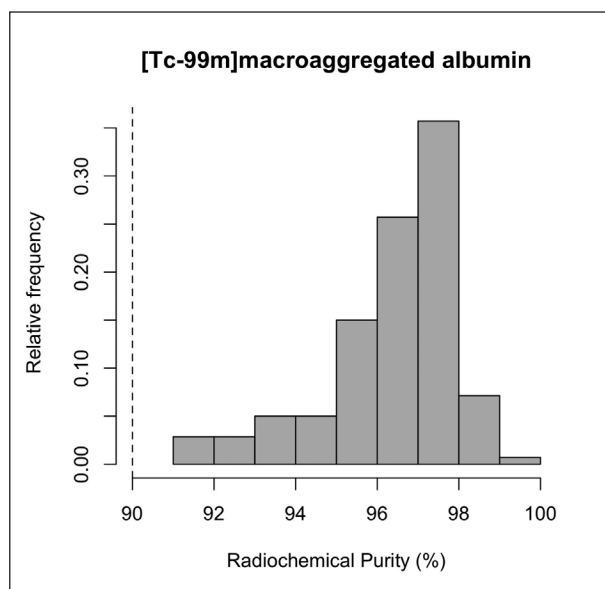


Figure 2. Relative frequency of radiochemical purity of 7 radiopharmaceuticals preparations. The vertical line represents the European Pharmacopoeia limits

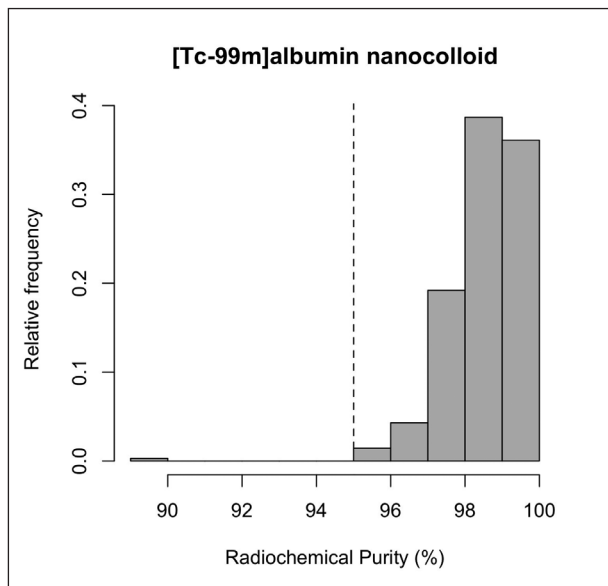


Figure 3. Relative frequency of radiochemical purity of 7 radiopharmaceuticals preparations. The vertical line represents the European Pharmacopoeia limits

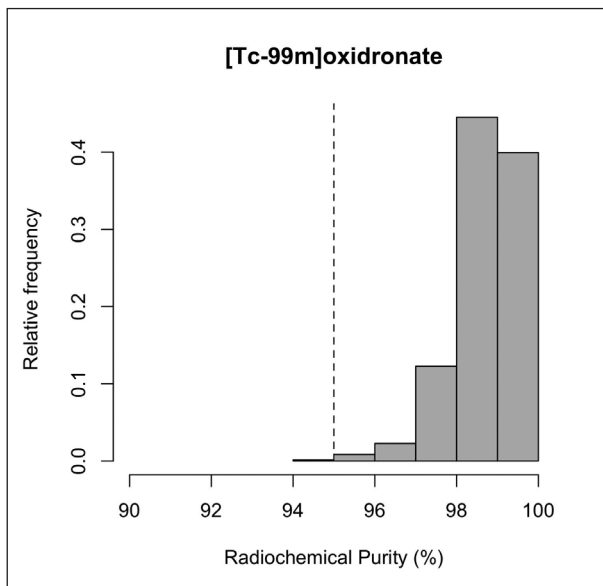


Figure 4. Relative frequency of radiochemical purity of 7 radiopharmaceuticals preparations. The vertical line represents the European Pharmacopoeia limits

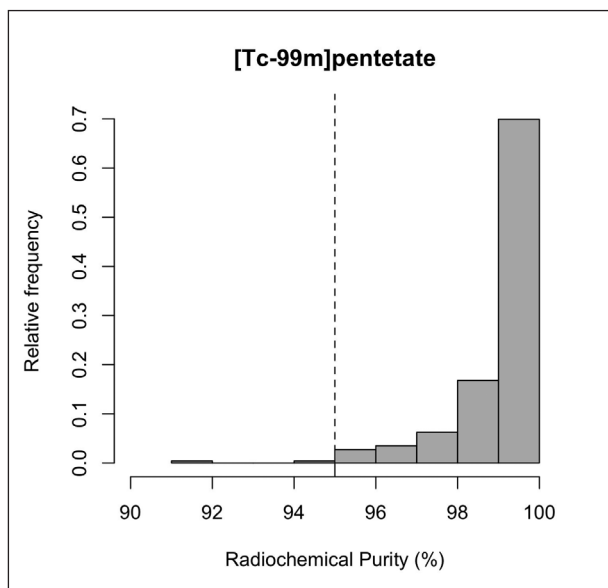


Figure 5. Relative frequency of radiochemical purity of 7 radiopharmaceuticals preparations. The vertical line represents the European Pharmacopoeia limits

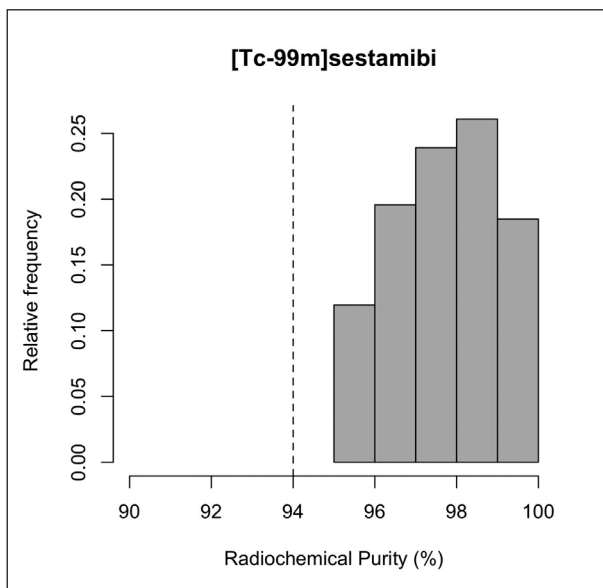


Figure 6. Relative frequency of radiochemical purity of 7 radiopharmaceuticals preparations. The vertical line represents the European Pharmacopoeia limits

differences between radiopharmaceuticals prepared in either 24 or 72 hours ($p=n.s.$) for all five radiopharmaceuticals. None of the 459 preparations were found to be beyond the criteria of quality of RCP.

All 4 technicians involved in the preparations performed the same number of preparations using the same varieties of radiopharmaceuticals.

In all 2280 preparations, all 4 technicians pro-

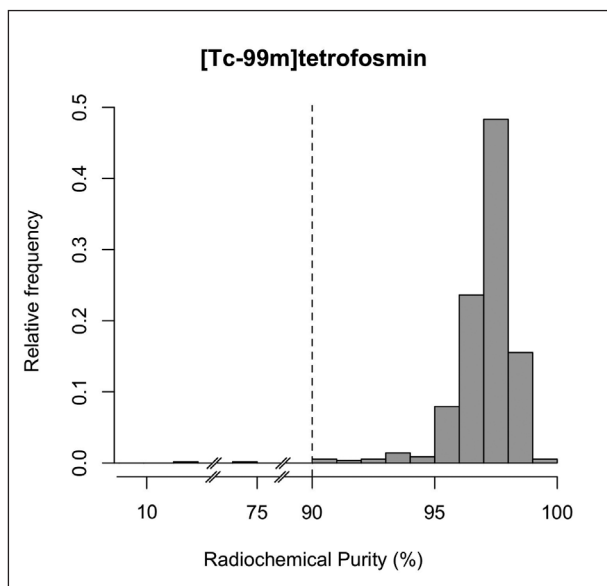


Figure 7. Relative frequency of radiochemical purity of 7 radiopharmaceuticals preparations. The vertical line represents the European Pharmacopoeia limits

vided data that were comparable. Also, no differences were observed between the RCP of the 4 technicians involved. The cost analysis was performed taking into account the time used (average 20 minutes for each control), and the costs of materials and reagents (Table 4), at € 31,483.51 for the total of procedures performed. So the average expenditure for each test was € 13.81.

Discussion and conclusion

The Italian rules of Good Preparation of Radiopharmaceuticals in Nuclear Medicine (NBP-MN) (5) have highlighted the need to control the process of production of ^{99m}Tc -labeled radiopharmaceuticals through a program of quality assurance, where radiochemical purity is a fundamental parameter in compliance with European directives and guidelines.

Radiopharmaceuticals labelled with ^{99m}Tc were prepared from kits and generators, both provided with AIC and detailed descriptions regarding the determination of RCP by the user. Even in the kit, the radiochemical reaction is complex (14-16) and involves stoichiometry, storage temperature of the pharmaceutical before and after labeling, reconstitution volumes, maximum and minimum activity of ^{99m}Tc used, radiochemical impurities (16). In particular, the ^{99m}Tc -tetrafosmin and ^{99m}Tc -oxidronate were frequently prepared in our center using the maximum activity in the required volume. This action does not alter RCP values.

We found also that the RCP was unaffected by accidental storage of the pharmaceutical at room temperature for a time lapse of 72 hours; ^{99m}Tc -tetrafosmin and ^{99m}Tc -macroaggregated albumin analyzed after this event was found within RCP limits for human use. Regarding preparations made 72 hours after the first elution of ^{99m}Tc (Table 3), we did not find any significant differences when compared to radiopharma-

Table 3. Summary of results for Radiochemical Purity and Impurity determinations after 72 hours of the first elution (n=459)

Radiopharmaceutical	N° tested	Radiochemical Purity %			$^{99m}\text{TcO}_4^-$ %			$^{99m}\text{TcO}_2$ %			N° of failures
		Range	Median	1q-3q	Range	Median	1q-3q	Range	Median	1q-3q	
^{99m}Tc -albumin colloid	104	95.7-100	98.4	97.8 -99.2	0 - 4.3	1.6	0.8 - 2.3	-	-	-	0
^{99m}Tc -oxidronate	159	97.3-100	98.8	98.3 -99.3	0 - 2.1	0.8	0.4 - 1.1	0 - 1.7	0.4	0.1 - 0.7	0
^{99m}Tc -sestamibi	6	95.1-98.2	96.9	95.9-98	1.8 - 4.9 (b)	3.1 (b)	2- 4.1 (b)	-	-	-	0
^{99m}Tc -albumin aggregated	42	93.2-98.3	97	96.1-97.6	1.7-6.8 (c)	3 (c)	2.4-3.9 (c)	-	-	-	0
^{99m}Tc -tetrafosmin	141	91 - 99.3	97.3	96.6-97.8	0 - 7.2	0.1	0 - 0.2	0.1 - 4.9	2.5	1.9 - 3.2	0
^{99m}Tc -diethylene triamine pentaacetic acid	7	96.2-100	99.6	99.2-100	0 - 1.1	0	0 - 0.5	0- 2.9	0	0 - 0.3	0

(a) $^{99m}\text{TcO}_2 + ^{99m}\text{Tc} \text{ II}^\circ$ HMPAO; (b) Total radioactivity impurity; (c) Radioactivity passing the membrane

Table 4. Analysis of costs in 2280 RCP quality control (3 years)

Radiopharmaceutical	Solvent cost for test €	Chomatoprahy paper cost for test €	Materials cost for test (solvent and chromatography paper) €	Labor cost for test €	Total cost for test €	N° test	Total cost in 3 years €
^{99m} Tc-albumin colloid	0,06	0,91	0,97	10,50	11,47	349	4003,03
^{99m} Tc-oxidronate	0,06	1,70	1,76	9,80	11,56	701	8103,56
^{99m} Tc-exametazime	0,29	5,10	5,39	11,55	16,94	169	2862,86
^{99m} Tc-sestamibi	0,04	2,50	2,54	24,50	27,04	92	2487,68
^{99m} Tc-albumin aggregated*	2,00		2,00	2,91	4,91	140	687,40
^{99m} Tc-tetrafosmin	0,11	2,55	2,66	14,70	17,36	567	9843,12
^{99m} Tc-diethylene triamine pentaacetic acid	0,06	1,70	1,76	11,55	13,31	254	3380,74
^{99m} Tc-dimercaptosuccinic acid	0,29	2,55	2,84	11,55	14,39	8	115,12
						Total cost in 3 years €	31483,51

*Isopore membrane filters 3 µm

ceutical prepared using more freshly eluted technetium solution, and if we avoided the preparation of the critical kit (^{99m}Tc-exametazime (HMPAO)) with 72 hours elution.

The errors found in QC, while representing a very small percentage of the total (6/2280), make it clear that while the preparations were all acceptable (except nanocoll), quality controls that require greater manual ability and more laboratory practice can result in a certain number of random human gross errors. In our ISO9001 certified quality system, we planned two repetitions of the quality control measures when the RCP appears below limits. Moreover, when the second repetition results were below the limits, the preparation was not administered to patients and was analyzed for each single variable of the process. In particular, two gross errors in q.c. of ^{99m}Tc-tetrofosmin were due to the exchange of solvents used in the eluent phase. Following the non compliance of ^{99m}Tc-toxidronate and ^{99m}Tc-diethylene triamine pentaacetic acid by the dose calibrator, we created a profile of imprecision varying the measurement time and establishing a coefficient of variation ≤5%. In this way, the measurements of low radioactivity (approximately 1 MBq) were accurate. The measure “cut and count” was raw and therefore limited the detailed analysis of the radioactive molecules present in the preparation, but remained suffi-

cient to routinely measure RCP (12). Following the quality control failure on the ^{99m}Tc-albumin colloid (nanocoll), we immediately notified the manufacturer, who instructed us to prolong the incubation time (from 30 to 60 minutes). This has resulted in values within the limits of RCP as well.

In our department, technicians participate in a continuous training program that includes 50 hours of CME (Continuing Medical Education) each year (18-20). For these reasons, there were no major differences between the 4 operators in regards to the production of radiopharmaceuticals.

In the present study the evaluation of the RCP results show a limited number of unacceptable preparations attributable to gross errors. Excellent performance in labelling radiopharmaceutical seems to be attributable to the training and experience of personnel, organization of production and quality controls, high reliability and stability of the industrial reagents. The expenses incurred in carrying out the quality controls of the RCP amounted to € 13.81/test (16% for materials and 84% for labor cost). This expenditure does not affect the overall cost of production and guarantees the quality of the radiopharmaceutical product. In conclusion, the preparations of radiopharmaceuticals labelled with ^{99m}Tc can be considered safe and this may lead to optimization of the frequency of RCP (e.g. once a

week for consolidated preparations, but on every preparation for new radiopharmaceuticals and in the cases of new operator and bad quality images), since the risk of the preparations not in compliance has been eliminated to zero. This would allow an appropriate balance between the need to keep the process under control and clinical economic sustainability. Our results suggest that the continuous improvement of the technologist's skills in the labelling procedures could optimize the quality control procedures frequency, ensuring both patient safety and a more rational management of resources for economic sustainability.

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Correspondence:

Claudio Maioli, BD, PhD

Unit of Nuclear Medicine, San Paolo Hospital

Department of Health Sciences, University of Milan

Via A. Di Rudini, 8 - 20142 Milan, Italy

Tel. +39/0281844320

Fax +39/0281844062

E-mail: claudio.maioli@unimi.it