Institut de radiophysique

RADIOPHARMACY COURSE

Quality control of radiopharmaceutical preparations (kits)

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Summary

CHAPTER • 1

INTRODUCTION

Goal
• *Know the different types of products used in radiopharmacy*
• *Understand the purpose of achieving QC*

1. Introduction

Radiopharmacy is defined by the use of unsealed radioactive sources for the preparation of radiopharmaceutical drugs (RPH) for nuclear medicine.

Swissmedic defines radiopharmaceuticals as "drugs that contain radionuclides whose radiation is used for diagnostic or therapeutic purposes" [1].

In Switzerland, it can be considered that 3 types of radiopharmaceutical drugs are used:

- **ready-to-use RPHs** (e.g. Datscan®), authorized in Switzerland or imported under a special authorization issued by Swissmedic;
- **preparations** (kits) that are authorized in Switzerland (e.g. Nanocoll®) or imported under a special authorization issued by Swissmedic;
- **manufacturing or synthesis** using products not registered in Switzerland and governed by a manufacturing authorization issued by Swissmedic ("formulas" according to Article 9, paragraph 2 LPTh, for example "formula magistralis").

2. Why is there need for quality controls in radiopharmacy?

The quality controls carried out in radiopharmacy make it possible to guarantee the quality of the product injected into the patient. For this purpose, the controls to be performed vary according to the type of RPH used.

For example, for ready-to-use products, the quality of the product is guaranteed by the supplier. The purpose of the check is therefore to verify that the supplier has sent the right product and that the information provided is correct. For example, check lot number, expiry date and activity.

For preparations, the aim is to verify that the radiolabeling has gone well. For example, the radiochemical purity and also the pH (if requested) will be checked.

CHAPTER• 2

LEGAL SITUATION

Goal

- *Know the different texts relating to quality controls*
- *Know how to find the information needed to carry out quality controls*

1. Directive L-10-06: Requirements for the preparation of radiopharmaceuticals

The directive only concerns products registered in Switzerland, this means ready-to-use RPHs and preparations (kits). A paragraph is dedicated to quality controls.

Let's go through each of the points in directive L-10-06 [2] and explain them:

1. "Each MRP shall be the subject of instructions for preparation and quality control. These instructions are included in the authorized company information and possibly additional internal instructions "[2].

➔ *This means that the supplier must describe in the package leaflet of his product how to carry out the preparation and quality control. This information can be supplemented by in-house instructions.*

2. "Quality control must be carried out in accordance with professional information or the Pharmacopoeia" [2]

➔ *Only the methods of preparation and quality controls proposed in the professional information (this point will be detailed below) and the Pharmacopoeia are validated. Centers without Swissmedic manufacturing licenses must comply with them.*

➔ *Centers with a Swissmedic manufacturing license may use another method. This method must be validated and must provide results at least equivalent to the official method.*

3. "We need to define a quality assurance system and designate the people responsible for the quality of the MRP. These are responsible for controlling the marking process and releasing the product for the intended application"

4. "The release of each preparation is based on a written record including the result of the relevant quality control."

➔ *The release of a preparation must be registered in written form. It must mention the results obtained by quality control.*

2. Pharmacopoeia

There are 2 types of Pharmacopoeia valid in Switzerland:

- the European pharmacopoeia;
- the Swiss Pharmacopoeia (Pharmacopea Helvetica).

3. Professional information

This is the information in the box containing the product. It is also called: SPC (Summary of Product Characteristics). The professional information contains all the information relating to the labeling of the product, its preservation before and after the labeling, the method to carry out the quality control as well as the requirements to release the product.

We can also find them:

- on the Swissmedic website: http://www.swissmedicinfo.ch/default.aspx;
- on the Swiss Compendium of Medicines: https://compendium.ch;
- on the company's website.

 Always make sure that the version you rely on is the latest version.

4. Other regulatory texts

4.1. Texts relating to medical applications and radiopharmaceuticals

- Verordnung über die Bewilligung im Arzneimittelbereich, AMBV (812.212.1).
- Verordnung über die Arzneimittel VAM (812.212.21).
- Bundesgesetz über Arzneimittel und Medizinprodukte, HMG (812.21)
- Guide to Good Practice for the Preparation of Medicinal Products in Healthcare Establishments PE 010-4.
- PICS GMP Guides: https://www.picscheme.org
- Guidelines on current Good Radiopharmacy Practice in the Production of Radiopharmaceuticals; European Association of Nuclear Medicine.
- EU Guidelines to Good Manufacturing Practice; Medicinal Products for Human and Veterinary Use, Annex 1: Manufacture of Sterile Medicinal Products (25-11-2008), http://ec.europa.eu/health/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf.
- Monographien der Europäischen Pharmakopöe

4.2. Texts related to radiation safety

- Wegleitung L-06-01. Dosimetrie beim Umgang mit offenen radioaktiven Stoffen.
- Verordnung des EDI über die Personen- und Umgebungsdosimetrie (Dosimetrieverordnung) 814.501.43
- Strahlenschutzverordnung, 814.501

CHAPTER • 3

DIFFERENT TYPES OF QUALITY CONTROLS

Goals

- *Know the different types of existing quality controls and their objective (s)*

1. Physical controls

The objective of the physical checks is to highlight any isotope error or the presence of other radioactive impurities, which would in the first case lead to the need to repeat the examination and in the second case cause an abnormally high irradiation of the patient and images of poorer quality.

1.1. Identification of the isotope

The physical period is characteristic of the element. The isotope can be identified by establishing the decay curve and calculation of the half-life of the isotope. The isotope can also be identified by its energy and radiation, for example by gamma spectrometry.

1.2. Radionuclidic purity

The radionuclidic purity or RNP is defined in the European Pharmacopoeia [3] as the ratio of the radioactivity of the radionuclide considered to the total radioactivity of the source in percentage.

This is for example the determination of molybdenum in the eluates of Technetium.

1.3. Activity of the source

Activity is the number of nuclear decays or transformations occurring per unit of time. It is expressed in Becquerel (Bq), which corresponds to a transformation per second.

Activity is measured using a calibrated and regularly monitored dose calibrator. Measuring an activity is always linked to a date and time.

Regulations relating to dose calibrators and QC of dose calibrators

- Wegleitung L-09-01, Qualitätssicherung von Aktivimetern.
- Verordnung des EJPD über Messmittel für ionisierende Strahlung, StMmV (941.210.5).

1.4. Radioactivity concentration

The radioactive concentration is the radioactivity of a nuclide relative to the volume unit of the solution. It is expressed in Bq/l.

1.5. Specific radioactivity

The specific radioactivity is the radioactivity of a nuclide relative to the mass unit of the element or chemical form considered (Bq/kg or Bq/mol). Specific activity is a key factor to be determined for functional investigations to quantify receptor sites, transporters, enzymes.

2. Chemical controls

2.1. Radiochemical purity (RCP)

Radiochemical purity or PRC is defined by European Pharmacopoeia as, for a given radionuclide, the ratio, expressed as a percentage, between the radioactivity attributable to the indicated chemical form and the total radioactivity attributable to that radionuclide in the radiopharmaceutical preparation. The list of potential radiochemical impurities to be considered is given in each specific monograph, with the corresponding limits "[3].

→ This is the fraction of a given radionuclide present in the expected chemical form relative to the total activity of that same radionuclide in the source.

It is calculated as follows:

$$\text{RCP (\%)} = \frac{\text{Activity due to the isotope in the expected chemical form}}{\text{Total activity due to the isotope in the source}} x\ 100$$

For example, in the case of kits labeled with technetium, it is in particular to look for free pertechnetate (TcO^{4-}) and hydrolysed reduced technetium (Tc-R, TcO_2).

To better understand the calculation, we can write the formula in this form:

$$RCP\ (\%) = \frac{RPH}{\text{RPH} + TcO_4^{2-}(\text{not labeled}) + TcO_4^{-} + TcO_2}\ x\ 100$$

Labelled radiopharmaceutical (TcO_4^{2-} in labeled form)

Total activity of the source

It is important to measure the radiochemical purity, because when the radionuclide is not in the expected chemical form, it may have a different biological behavior from that of the RPH. This can lead to unwanted irradiation of the patient and poor quality images.

For example, free pertechnetate ion (TcO^{4-}) will bind to the thyroid, stomach and salivary glands and reduced hydrolyzed technetium (TcO_2) in the liver and spleen. These are the 2 main species sought for technetium kits.

2.2. Chemical purity

Chemical purity is the ratio, expressed as a percentage, of the mass of material present in the chemical form indicated to the total mass of material contained in the source.

This is for example the quantification of aluminum in the technetium eluates. Aluminum is sought after because it is toxic, it can alter the quality of the preparations and modify the biodistribution of the RPH. To carry out this check, quick kits are available, for example the kit Aluminum Breakthrough Kit laboratory Biodex®. The latter proposes to deposit a drop of eluate on an indicator paper which causes a colored reaction. In parallel, a standard containing the limit

concentration of aluminum is also deposited. The result is read by comparison of the coloring of the 2 drops.

2.3. pH

For each RPH, there is a pH range within which stability and labeling are optimal. pH measurement is easily and quickly done by placing a drop of radiopharmaceutical on pH paper and reading the result immediately.

This test is not always mandatory; however, it is simple and easy to perform. It can detect product inversions (the kits do not all have the same pH), detect possible kit unconformities, and in some cases it can highlight lack of certain reagents.

For example, in the case of Ceretec®, when the cobalt solution has been introduced the pH of the solution is between 5.0 and 8.0 and the solution is pale straw yellow. The non-stabilized product (before introduction of the cobalt solution) has a pH of between 9.0 and 9.8.

2.4. Isotonicity

A solution is isotonic when it has the same osmotic pressure as the blood. Physiologically, the water contained in a medium will always dilute the most concentrated medium. If a hypertonic fluid is injected intravenously, the surrounding tissue will migrate into the plasma compartment creating dehydration of the surrounding environment. If the fluid is hypotonic, the water will leave the plasma medium to go into the surrounding tissues creating edema. This test is not performed by the user in current practice, isotonicity is guaranteed by the company.

3. Biological controls

3.1. Sterility

An injectable solution must be sterile. Performing sterility control before injection for RPH is impossible considering the half-life of the product. Sterility is guaranteed by the vendor for ready-to-use kits and MRPs until end of shelf-life of the labelled product.

The sterility of the RPH is also guaranteed by the validation of the process of preparation and the operators (Media Fill tests), the rigor of the handling and the quality of the environment: environmental control (class A), environmental controls (samples of surface and air, particulate counts).

3.2. Apyrogenicity

A pyrogen-free product is a product that does not give a fever. The test consists of highlighting any bacterial endotoxins. These are chemicals from the outer membrane of gram-negative bacteria. These are lipopolysaccharides which can be released during the death and decomposition of the bacterium for example under the effect of sterilization. Endotoxins, when injected, can cause a toxic reaction in humans (inflammation, nausea ...) or even anaphylactic shock in the worst case.

The reference test for endotoxins is the LAL (Limulus Amoebocyte Lysate) [3] test, which consists of the formation of a gel when the lysate is brought into contact with endotoxins. This test is not very practical to perform, there are many false positives and false negatives. It is poorly realized in practice. Other systems have been put in place to detect endotoxins, however the LAL test remains the reference.

Apyrogenicity is guaranteed by the supplier for ready-to-use RPH and kit radiopharmaceuticals.

4. Galenic controls

4.1. Organoleptic characters

Organoleptic controls include color, appearance, abnormal presence of particles, etc. Parental solutions must in general be clear and particle-free. The simple observation of the preparation makes it possible to highlight the presence of particles in the solution, for example bits of polymer coming from the coring (piercing) of the septum.

The color of the product can also give information about successful preparation. For example, Ceretec® is a colorless solution. When stabilized with cobalt, it takes on a pale yellow color. Ceretec® exhales after 30 minutes, Ceretec® stabilized (Cerestab®) expires after 5 hours.

In radiopharmacy, the observation of the solution can be difficult given the radiation protection equipment used (colored led glass). When this control is introduced in everyday practice, one must be aware that it exposes the operator to radiation and that radiation protection measures must be taken (observation behind a leaded screen, manipulation with the help of tweezers, etc.).

4.2. Galenic form

Different pharmaceutical forms are used in radiopharmacy. For example, nanocolloids are used to perform radiosynoviortheses, suspensions for Sirspheres and Teraspheres, and finally macroaggregates of human albumin for pulmonary exploration. For the latter, the size of the maccroaggregégats present in the solution directly determines the quality of the examination.

5. Summary

Table 1. Summary table of the various quality controls carried out in radiopharmacy.

Type of quality control	**Test to realize**
Physical controls	Identification of the isotope
	Radionuclidic purity (RNP)
	Activity of the source
	Radioactivity concentration
	Specific radioactivity
Chemical controls	Radiochemical purity (RCP)
	Chemical purity
	pH
	Isotonicity
Biological controls	Sterility
	Apyrogenicity
Galenic controls	Organoleptic characteristics
	Galenic Form

Summary of the checks to be carried out routinely in the nuclear medicine centers:

Table 2. Quality controls done in daily practice.

Product type	**Control**	**Guaranteed by company**
Kit	pH (if requested) Organoleptic characteristics (visual control) **Activity** **Radiochemical purity (RCP)**	Sterility, Apyrogenicity, chemical purity
RPH ready to use	**Product check** Organoleptic characteristics Isotope identification **Activity**	Isotope identification Sterility, apyrogenicity Radionuclidic purity Chemical purity
Generator eluate	Organoleptic characteristics pH (if requested) **Activiy** **Elution yield** Aluminium (if requested)* **Radionuclidic purity (ex. Molybdenum content)**	Sterility, apyrogenicity

(Also done by the company)*

Note:

- *This table is to be adapted according to the products you use. Mandatory quality checks are given in the SPC for each product.*

- *Quality controls in bold are those that we recommend to realize for each product.*

- *The verification of the organoleptic characters and the measurement of the pH leads to the irradiation of the operator. A reflection based on the benefit / risk ratio of these controls must be realized.*

- *The sterility and apyrogenicity of the kit are guaranteed by the supplier. The latter does not guarantee these parameters for the final preparation. This is why the training of operators, the validation of the process and the operators, the control of the preparation environment (cleanings and regular inspections) are essential in radiopharmacy.*

CHAPTER • 4

QUALITY CONTROL IN DAILY PRACTICE

Goals

- *Know for each type of RPH that you use what controls you need to perform*

This chapter describes the controls to be performed for the products used in your services.

For ready-to-use radiopharmaceuticals, you need to check for consistency of the information indicated by the company.

For preparations (kits) the following checks may be carried out:

- radioisotope: identification and activity;
- radiopharmaceutical: organoleptic characteristics, pH, activity and radiochemical purity.

1. Ready-to-use radiopharmaceuticals

Control consists in verifying that the delivered product corresponds to the delivery order and the purchase order.

We will therefore check:

- the product type;
- the lot number;
- the expiration date;
- the theoretical activity indicated on the product and on the delivery note.

We will also perform a measurement of the activity. By convention, a deviation of up to 10% from the calibration activity is accepted.

2. Radiochemical purity testing of kit radiopharmaceuticals

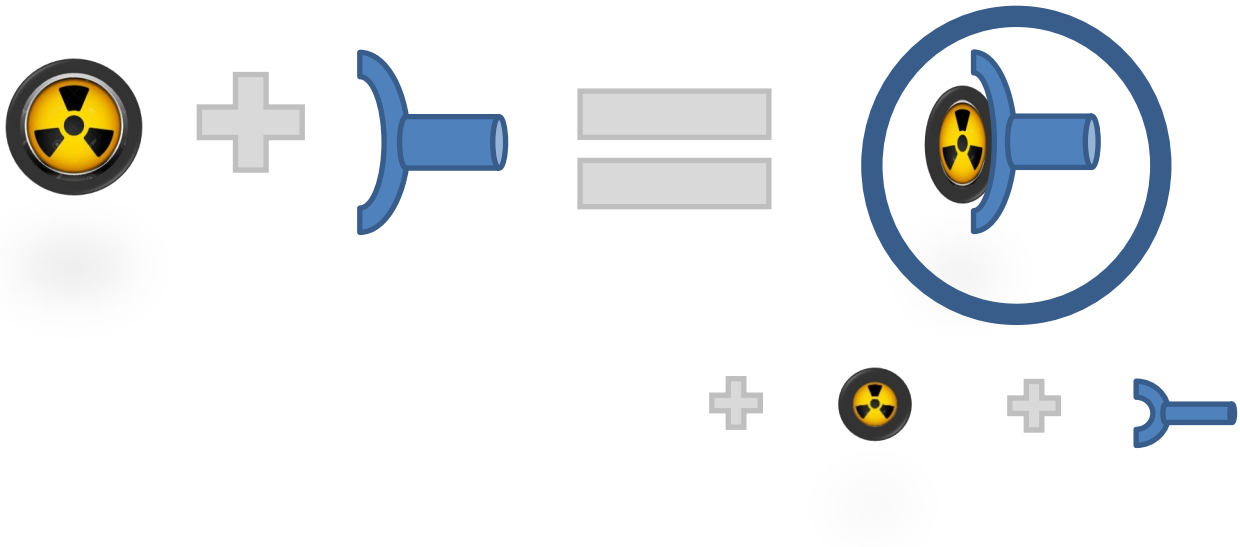
In the case of a preparation, a kit supplied by the supplier is marked in the service with a radioisotope eluate (normally 99mTc form a generator).

Kits must be checked at the time of receipt: the agreement between what has been received, the information on the packing slip and what has been ordered must be checked: product type, batch number, expiry date must be checked.

When checking a preparation, the objective is to check if the right product has been marked, if the marking has gone well and if the traceability information is correct. The organoleptic properties of the preparation can also be checked: color, appearance, clarity and presence of particles, and also pH and RCP.

2.1. Why do we check the radiochemical purity?

The labeling of a kit is a chemical process that can be illustrated as follows:



A molecule is labeled with a radioisotope to obtain the RPH. The kit contains all the non-radioactive components necessary for the formation of the RPH with good labeling efficiency. It contains the carrier molecule (peptides, antibodies, etc.) and other substances that allow the labeling to be done correctly: reducing agents (stannous chloride), antioxidant (ascorbic acid / gentisic acid), buffer, and chelating agent; solubilize agents and freeze-drying agent. At the end of the labeling, we obtain the radiopharmaceutical drug (vector molecule + radioisotope), but also sometimes the free isotope because it is not fully complexed and the free vector molecule. The determination of radiochemical purity during quality control makes it possible to determine the proportion of each species in the final preparation and to verify that the marking has proceeded correctly.

2.2. Measurement of RPC

The radiochemical purity can be determined by HPLC or solid-liquid chromatography. Only the latter will be addressed in this course.

Solid-liquid chromatography consists of separating the constituents of a preparation according to their affinity for either the mobile phase or the stationary phase. It takes place in two steps:

- the realization of the chromatography;
- reading the results, 2 methods exist: scissors-cut method with reading with a dose calibrator or reading with a radioactivity scanner (TLC Scanner).

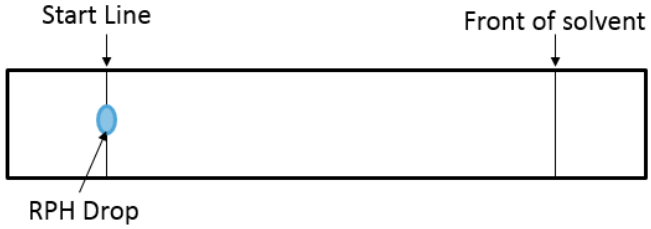
2.3. Realization of the chromatography

Step 1: Conditioning of the chromatography tank

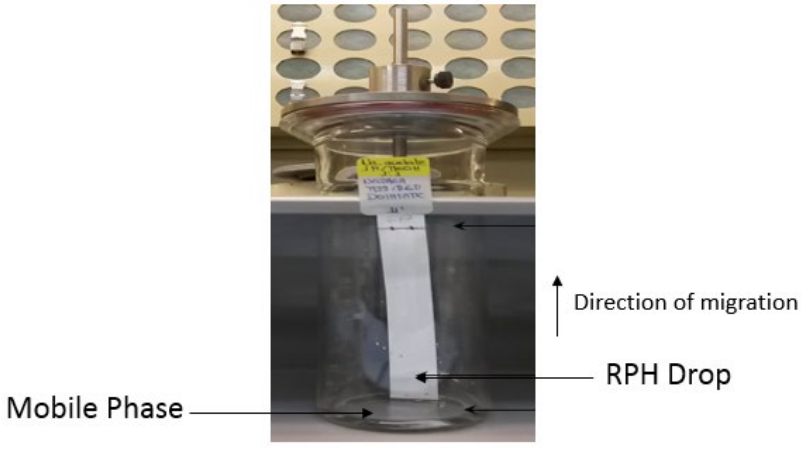
- Put about 0.5 cm of solvent height
- Close the tank
- Let stand about 15 minutes

Step 2: Migration

- Employ the appropriate paper (according to the SPC)
- Behind a lead screen, place a drop of preparation at the deposit line



- Allow to dry or not (according to SPC information)
- Insert the support in the tank
- The deposit line must not be in touch with the mobile phase
- Let migrate



During this check, you handle chemicals and radioactive products, always wear gloves, use forceps to manipulate chromatography plates and a leaded screen to protect yourself against external radiation.

Step 3: Reading of results

The reading of the chromatography plate can be carried out by means of a radioactivity scanner (TLC scanner) or by the scissor cut method.

Reading method with a radioactivity scanner (TLC scanner)

The chromatography plate is placed on a moving plate. Then, it is read over the entire length by the probe, a spectrum is recorded.

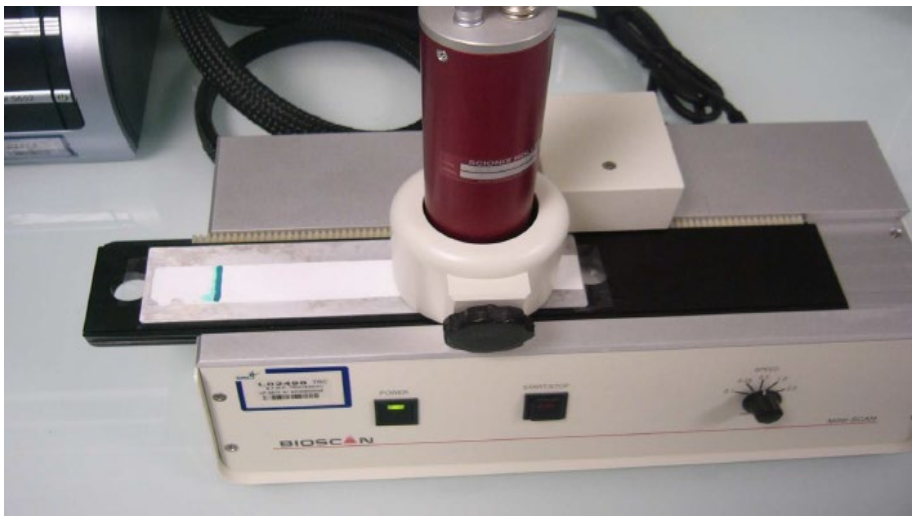


Figure 1. Reading of the chromatography stripe.

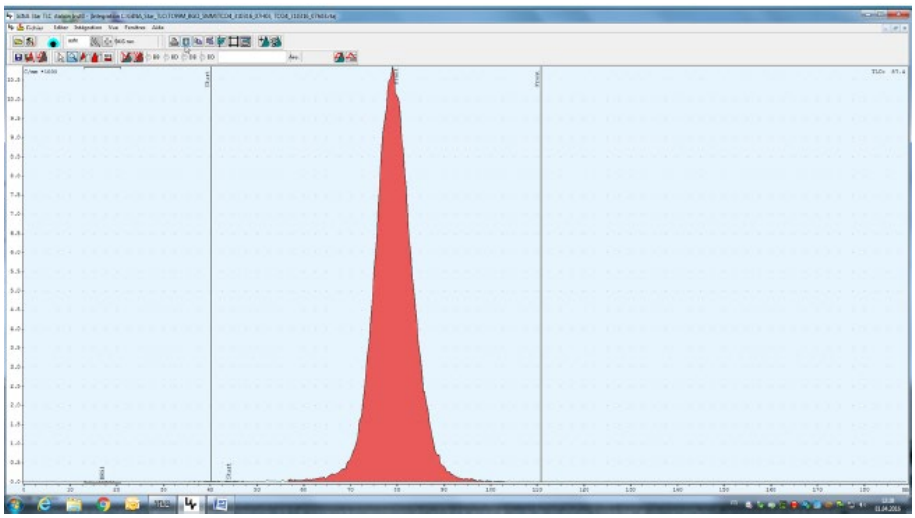


Figure 2. Spectrum obtained by reading a chromatographic plate for the measurement of radiochemical purity with a TLC scanner.

To exploit these results, it is enough to select the area where the activity due to the impurities appears and the one where the activity due to the MRP is traced. The scanner automatically calculates the percentage of impurity applying the following formula:

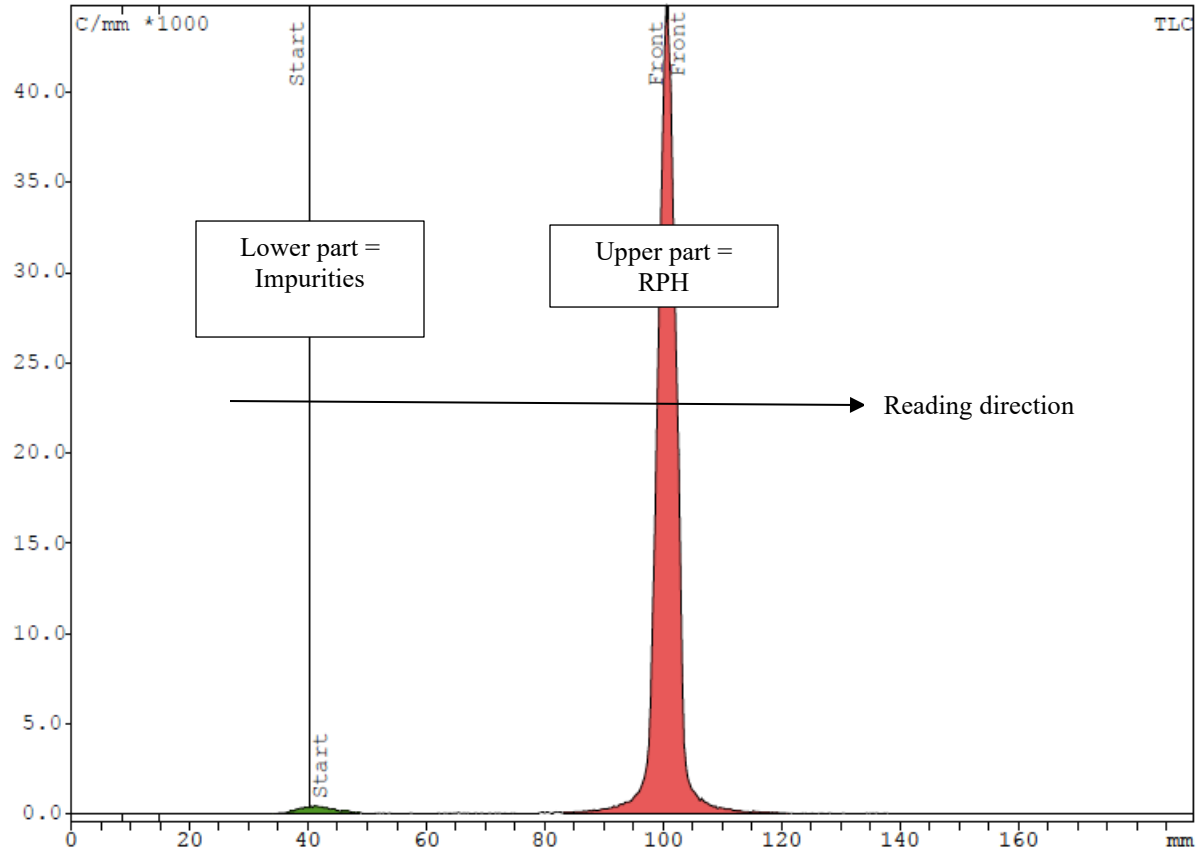
$$\text{RCP}\ (\%) = \frac{\text{Activity/counts of the RPH peak}}{\text{Total activity/counts on the plate}} \times\ 100$$

Example of Technescan® Sestamibi:

Information from SPC [6]

$$\% \text{ de technétium } [^{99m}\text{Tc}] \text{ sestamibi} = \frac{\text{Activité de la partie supérieure}}{\text{Activité des deux parties}} \times 100$$

Note: The radiochemical purity of technetium [^{99m}Tc] sestamibi should be ≥ 94%. If the radiochemical purity is less than 94%, technetium [^{99m}Tc] sestamibi should not be injected and the preparation should be discarded [6].



Intégration TLC

Substance	T/R mm	R/F	Début mm	Fin mm	Can	%Total %	Type	Aire Counts	%Aire %
Start	41.83	0.027	34.19	48.80	TLC	1.73	DD(	2965.9	1.75
Front	100.58	0.995	83.32	120.83	TLC	96.81	DD(	166435.8	98.25

$$RCP(\%) = \frac{98.25}{98.25+1.75} \times 100 = 98.25\% \Longrightarrow$$

RCP ≥ 94% → Product is ok

Reading method "scissors cut"

This method proposes to read the results using a dose calibrator. In this case, after the migration, the plate is cut in accordance with the SPC indications (in 2 for most MRPs and in 3 for the Myoview), then each part is measured with the dose calibrator. The radiochemical purity is then calculated manually:

$$\text{RCP (\%)} = \frac{\text{Activity of RPH containing part}}{\text{Total activity}} x100$$

For each of the plates measured, it is important to have identified the places to which the impurities and the RPH migrate. To avoid errors, it may also be interesting to put a mark on the plate to identify the top and bottom.

For some RPHs, it may be necessary to perform several chromatography's in parallel (ex. DTPA).

Example of Nanocoll®

After SPC [7]

Contrôle de la qualité

La qualité du marquage est déterminée par chromatographie ascendante sur couche mince (Varian SA TLC):
Support: Varian SA TLC (2 bandelettes de 12 cm; déposer une petite goutte de la préparation à 2,5 cm de l'extrémité inférieure).
Solvant: méthanol:eau, 85:15 v/v.

Quality control method

Durée: 25 à 30 minutes (à environ 7 cm de l'origine; retirer la bandelette de la cuve et la faire sécher).

^{99m}Tc (nanocolloïde): ≥95%.
Rf: 0,0 à 0,1.

Réalisation de la chromatographie

1. Verser le mélange 85:15 méthanol:eau jusqu'à 1 cm au-dessus du fond de la cuve pour chromatographie; couvrir la cuve pour permettre à la vapeur du solvant de se répartir de façon régulière.
2. Marquer un repère au crayon à 3 cm de l'extrémité inférieure d'une bandelette ITLC/SG, et un autre repère à l'encre à 15 cm au-dessus de cette ligne. Le trait au crayon indique le point où l'échantillon doit être appliqué. L'encre se met à migrer lorsque la phase mobile a atteint la ligne de couleur, indiquant la nécessité de stopper l'élution.
3. A 12 cm au-dessus du premier trait au crayon (Rf 0,8), marquer un repère supplémentaire au crayon (ligne de découpe).
4. Avec une seringue de 1 ml munie d'une aiguille, appliquer un échantillon de 10–20 µl de la solution injectable prête à l'emploi sur le premier trait au crayon. Ne pas laisser sécher le dépôt, mais placer immédiatement la bandelette dans la cuve à chromatographie et couvrir celle-ci. La bandelette ne doit en aucun point entrer en contact avec les parois de la cuve.

Remarque: 10–20 µl d'échantillon devraient donner un point de 7 à 10 mm de diamètre. Les échantillons de moindre volume donnent des résultats peu fiables concernant la pureté radiochimique.

5. Dès que le front du solvant a atteint le trait à l'encre, retirer la bandelette de la cuve et la laisser sécher.
6. Découper la bandelette à la position de découpe marquée au crayon et mesurer la radioactivité de chacune des deux parties au moyen d'un appareil de comptage adéquat. Le comptage pour les deux parties devrait être effectué en l'espace d'un minimum de temps et dans des conditions aussi similaires que possible. Le pertechnétate [^{99m}Tc] libre et d'autres complexes hydrophiles de technétium migrent (Rf 0,8 à 1,0).
7. Calculer la qualité du marquage au moyen de la formule suivante:

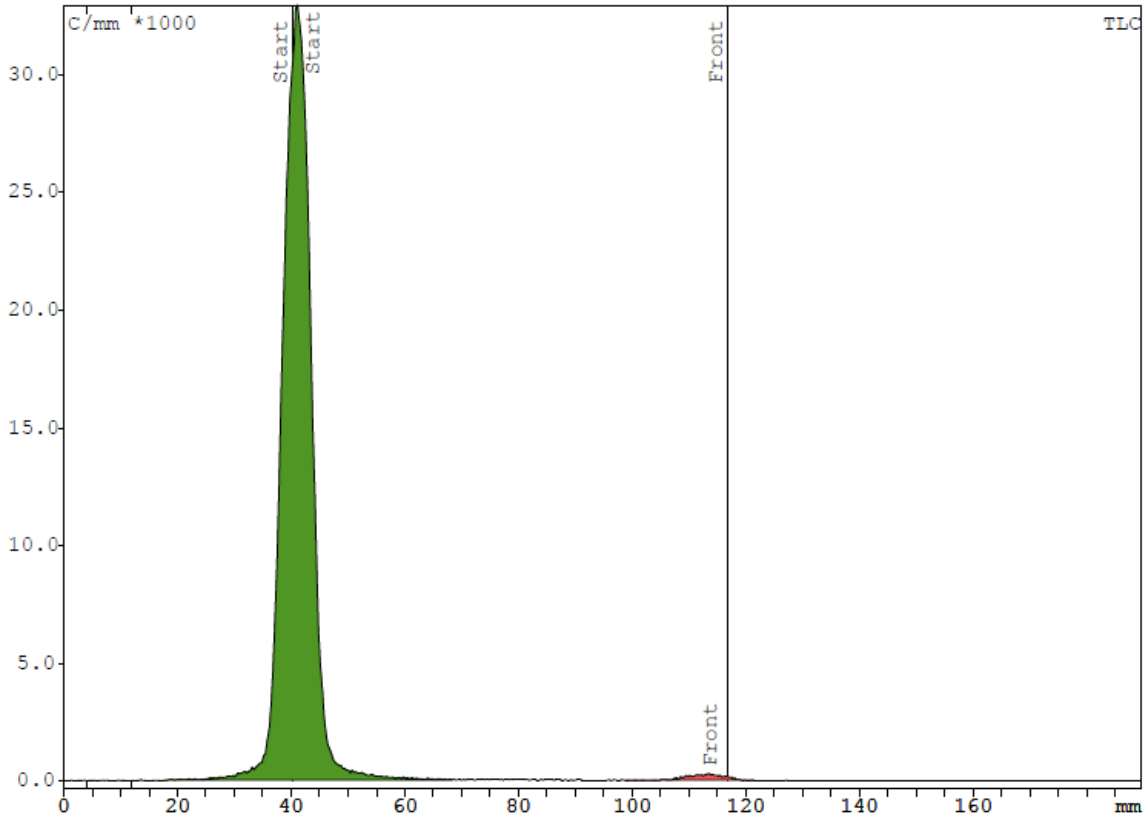
% Pureté radiochimique = activité partie inférieure : activité partie inférieure + supérieure × 100.

RCP calculation

La pureté radiochimique doit être de ≥95%.
Les solutions présentant une qualité de marquage inférieure à 95% ne doivent pas être utilisées.

Requirements

Reading with TLC scanner



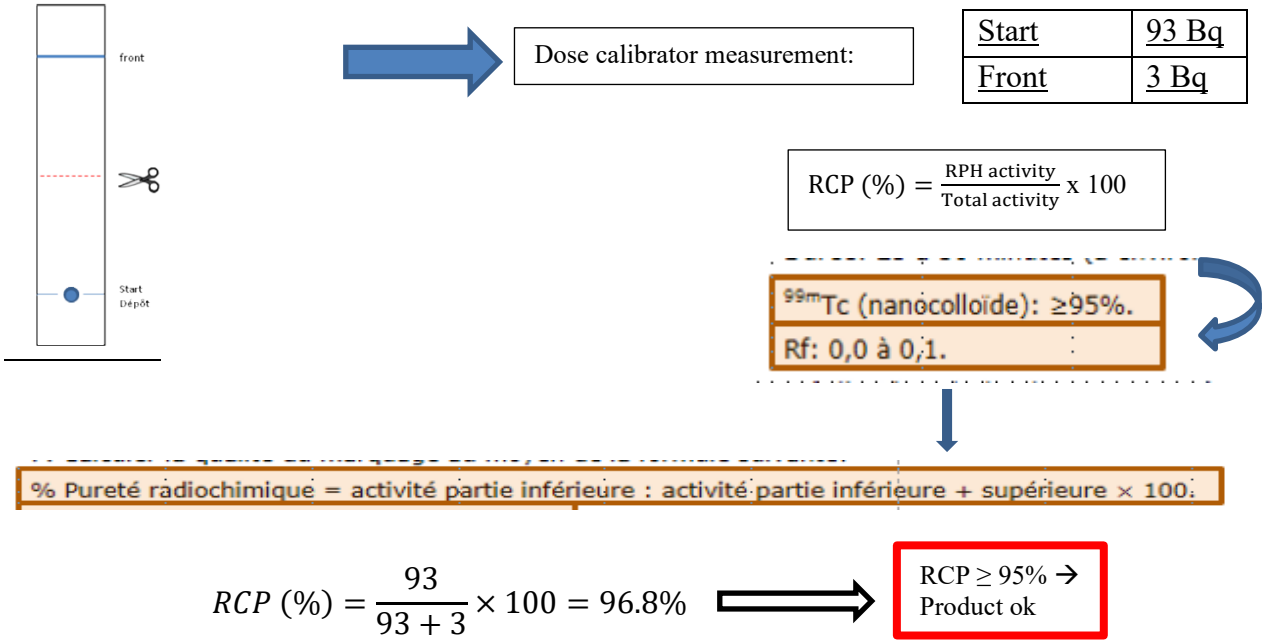
Intégration TLC

Substance	T/R mm	R/F	Début mm	Fin mm	Can	%Total %	Type	Aire Counts	%Aire %
Start	41.16	0.013	17.59	68.38	TLC	96.88	DD(	190933.4	98.94
Front	113.53	0.957	98.92	121.49	TLC	1.04	DD(	2046.8	1.06

$$RCP(\%) = \frac{98.94}{98.94 + 1.06} \times 100 = 98.94\% \Longrightarrow$$

RCP ≥ 95% → Product ok

Reading by scissor cut method



$$RCP\ (\%) = \frac{93}{93+3} \times 100 = 96.8\%$$

2.4. Effect of non-radiolabeled components

In most cases, the kits are marked with Tc-99m. In the eluate of the generator, Tc-99m is in the form of sodium pertechnetate. This species has no complexing properties, it must be reduced in order to be complexed by the vector molecule contained in the kit. The commercially available kits contain stannous chloride which will reduce the pertechnetate ion to a technetate ion which will be complexed with the carrier molecule. At the end of this reaction, we obtain the radiolabelled MRP but also the non-radiolabeled MRP and the non-complexed isotope.

The non-complexed isotope can then re-oxidize into free pertechnetate that will accumulate in the stomach, thyroid and salivary glands, or it can be reduced to TcO_2 that will accumulate in the liver and spleen. These species are responsible for unnecessary irradiation for the patient and can interfere with the quality of the image. Non-radiolabeled MRP competes with the labeled isotope and may be responsible for visible image abnormalities and increased image backgrounds. The measurement of the RCP performed aims to highlight abnormal rates of these species.

Industrial kits are designed to ensure successful RPH labeling. However, the marking procedure given in the SPC must be entirely respected.

3. Quality control of the generator

3.1. Should I use the first eluate of my generator?

For labeling of some RPH, suppliers require that the eluate comes from a generator whose last elution has been done less than 24 hours before. You can find this information in the preparation section of the SPC. Some suppliers elute generators before sending them to their customer. In these cases, the first generator eluate may be used to mark the RPHs.

We also draw your attention to the fact that it is also important to check with the company for specific supply situations (holidays and annual holidays).

3.2. Specifications of a generator solution

Example: In the RCP of the Ultratechnekow® generator taken as an example [7], the specifications of the eluate are given:

Spécifications

Spécifications de l'eluate

^{99m}Tc -pertechnétate comme solution claire, incolore, stérile, isotonique (quantité d'activité dépendante du temps d'elution et de l'activité nominale du nuclide mère ^{99}Mo).

pH:	5,0 – 7,0
Teneur ^{99}Mo:	normalement < 25 Bq/MBq ^{99m}Tc
Aluminium:	< 20 µg/ml
Substances oxydante:	aucune

We can therefore carry out the following quality checks:

- organoleptic characteristics
- pH
- measurement of the molybdenum content in the eluate (radionuclidic purity).
- aluminum limit test (chemical purity)

Information in the SPC [8]

Les éluats qui ne sont pas parfaitement limpides et incolores ne doivent pas être utilisés, et doivent être jetés!

Mandatory controls are therefore organoleptic controls (visual control). In current practice, the test of the molybdenum content and the aluminum test are often carried out on the first eluate of the generator.

The elution efficiency of the generator also provides information on the quality of the generator. The yield is even calculated automatically by some available radiopharmacy software.

4. Conclusion

Radiopharmaceutical labeling is dependent on many parameters: activity, specific activity, agitation modalities, temperature and heating time must be respected to ensure the success of the marking, hence the importance of carrying out the quality controls of radiopharmaceutical preparations to guarantee quality of the products injected to the patient. However, we must not forget the all other parameters to guarantee the quality of the final product:

- aseptic working method: control of the environment, control of premises and laminar flows, quality of aseptic work (validation of the process and the operator by Media Fill tests + control of specific preparations);
- control of measuring instruments: dose calibrator (daily QC, weekly, linear testing, intercomparisons, verifications) and TLC scanners (linearity and weekly QC).

Radiation protection rules must be followed during the performance of quality checks.

5. Summary

- *In this course we have discussed the different types of quality controls for RPHs performed in current practice.*
- *The described quality controls are important to guarantee good quality of the injected product (radiopharmaceutical).*
- *Measurement of the RCP and eventual measurement of the pH (not compulsory) can be used as an indicator that the marking went well. But keep in mind that there here is other parameters to be respected to guarantee final quality of the product. For example, RCP does not give any information about product sterility.*
- *Similarly, proper quality control should not be used for giving permission to inject expired products.*

BIBLIOGRAPHIE

[1] Swissmedic. HD-Guide complémentaire. Autorisation produit radiopharmaceutque ».

[2] Office fédéral de la santé OFSP. Directive L-10-06 : Exigences relatives à la préparation de produits radiopharmaceutiques.

[3] Pharmacopée Européenne. 5.19. Préparation extemporanée de produits radiopharmaceutiques. Edition 8.7, 2016.

[4] Dossier du CNHIM. Médicaments radio-pharmaceutiques : utilisation pratique. 1998, XIX, 5-6.

[5] Galy. G., Fraysse. M. Radiopharmacie et médicaments radiopharmaceutiques. 07/2012.

[6] Information professionnelle Technescan® Sestamibi. Mai 2014.

[7] Information professionnelle Nanocoll®. Avril 2018.

[8] Information professionnelle Ultratechnekow®. Novembre 2004.