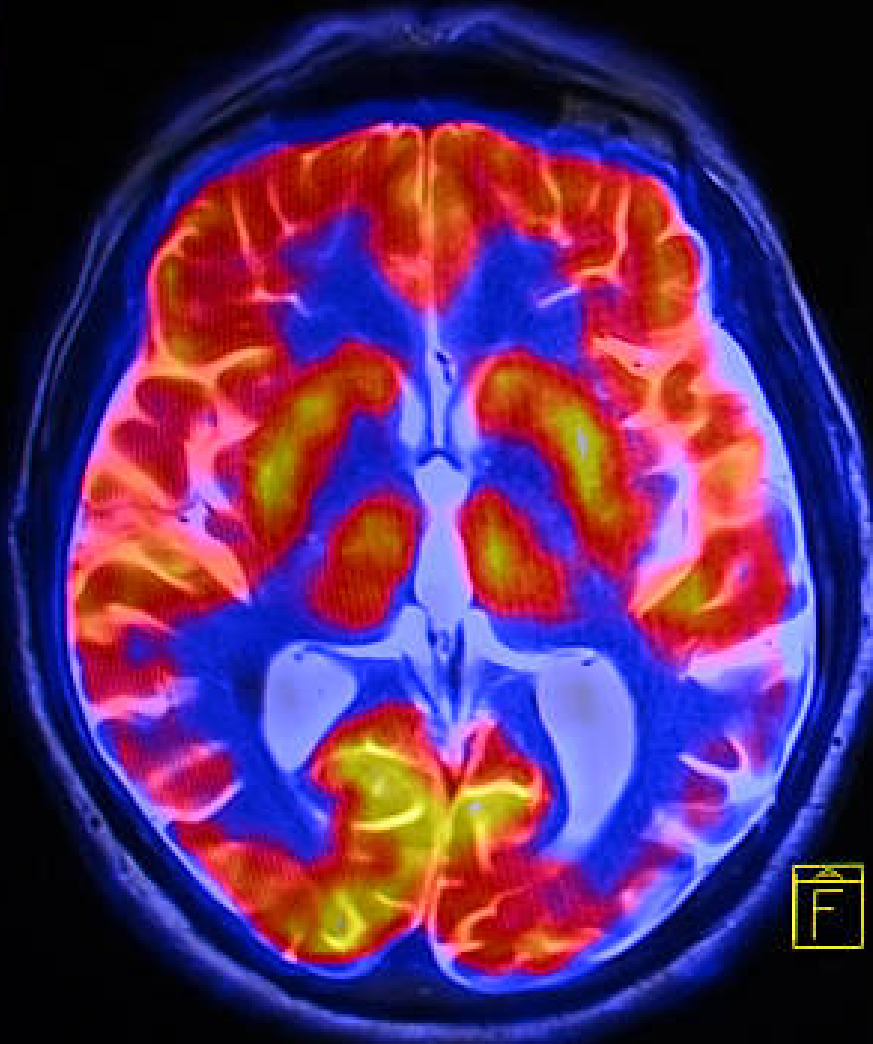


Radiopharmaceuticals in Nuclear Medicine



Part III: Radiopharmaceutical Products

- Categories of radiopharmaceuticals
- Labeling procedures: Preparation and Fabrication

Radiopharmaceutical Categories

General definition (PhEur) : medicinal products, which, when ready for use, contain 1 or more radionuclides included for a medicinal purpose

- Kit radiopharmaceuticals (to be reconstituted or combined with radionuclides)
- Ready to use radiopharmaceuticals (ex. therapeutic doses)
- Generators
- Radionuclide precursors (any radionuclide produced for radiolabeling of another substance prior to administration, ex. synthesis of Ga68 Peptides)

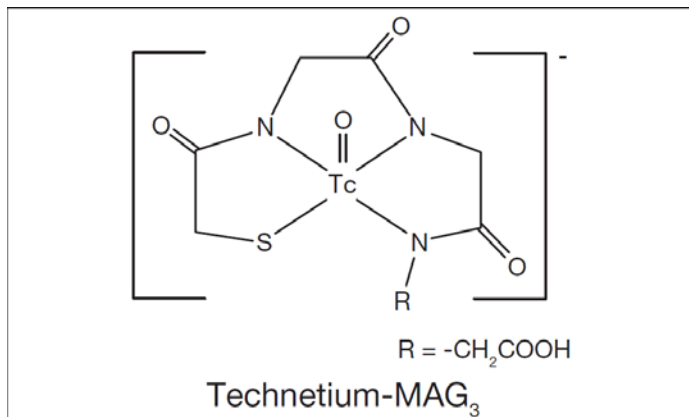
Kit Radiopharmaceuticals (ex. ^{99m}Tc Kits)

A Kit radiopharmaceutical is normally commercialized and the initial quality of the kit is guaranteed by the producer. The kit vial contains a lyophilisate with all components. The ^{99m}Tc is added to this vial.

- Active ligand system
- Reducing agents ($\text{Tc}^{99\text{m}}$ needs to be in reduced state for incorporation of metal complexes of ligands)
- Antioxidants
- Buffer components (physiological pH)
- Auxiliary ligand systems
- Auxiliary components

Kit MAG3 (^{99m}Tc Kit)

- Renal function imaging agent
- Cold kit with active substance 'tartrate' (lyophilisate)
- Addition of ^{99m}Tc eluate ($^{99m}\text{TcO}_4^-$) to the lyophilisate
- Labelling of the kit (heating and incubation)



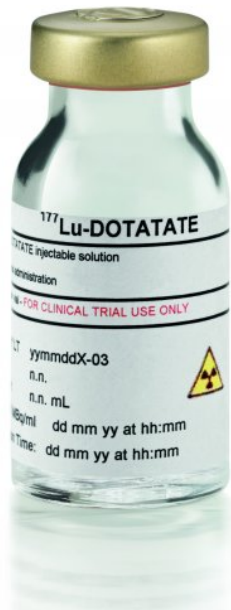
QC Recommendations for a Kit (^{99m}Tc Kit)

- Radionuclide purity
- Amount of Radioactivity
- Chemical Purity
- Radiochemical Purity
- Sterility
- Apyrogenicity (endotoxines)
- pH Value
- Radionuclide identity
- Particle Size

For commercial Kits, the chemical purity, apyrogenicity, particle size and pH value are generally guaranteed by the manufacturer.

Therapeutic Radiopharmaceuticals

The therapeutic pharmaceuticals often require a simple dose preparation. The product is delivered in its final form and only the patient syringe with the necessary activity needs to be prepared (measurement of dose in dose calibrator). No additional quality control (QC) required.



Generators

Generators are producing the eluates used for KIT preparations. In some cases, the elution can be used directly as a radiopharmaceutical (ex. $^{99m}\text{TcO}_4^-$). A generator is delivered with a so called SPC (summary of product characteristics) where the tests for the QC are described.

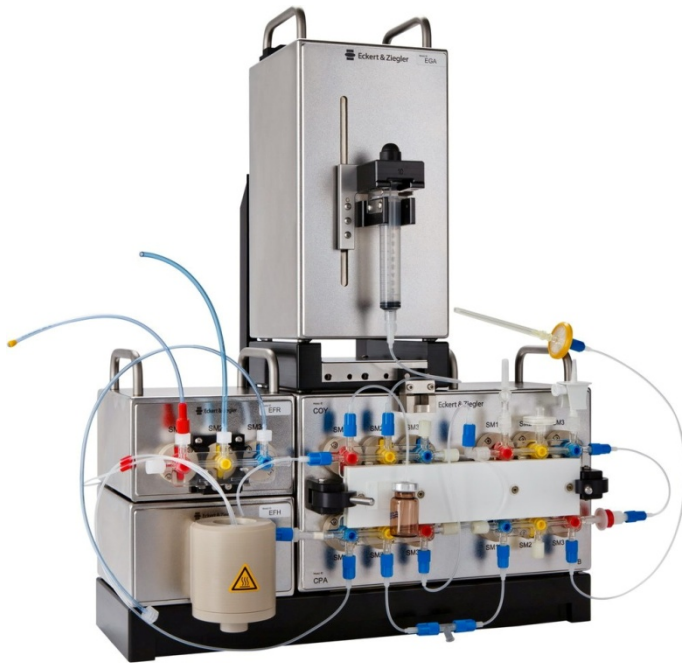
- ^{99m}Tc generators: to be checked for Molybdene 99 break-through
- ^{68}Ga generators: to be checked for Germanium 68 break-through
- Aluminum content
- pH



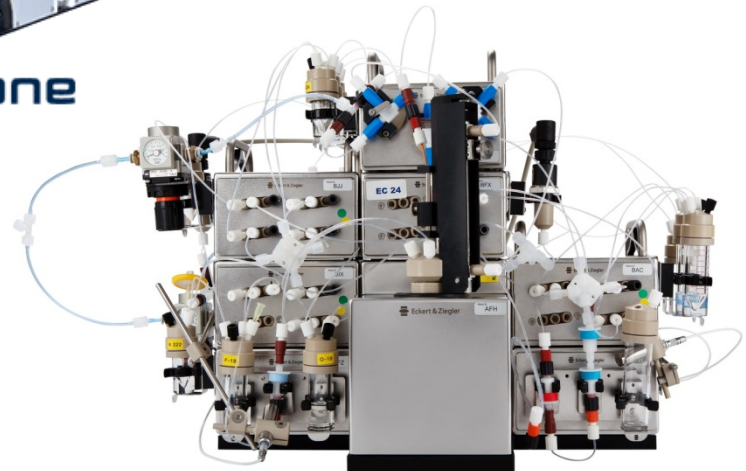
Radionuclide precursors, Synthesis Modules

Any in house fabricated radiopharmaceutical, ex. by synthesis modules.

Peptides or antibodies labelled with a radionuclide (ex. from a generator)



all in one



Radionuclide precursors, Synthesis Modules

Fabricated radiopharmaceuticals require special facilities, sophisticated QC instruments and special trained personnel.

In Switzerland, a fabrication of radiopharmaceuticals can only be done under the supervision of an EANM Radiopharmacist (or equivalent).

More exhaustive QC parameters are required that for Kit preparations:

- pH
- Sterility and endotoxins (validation batches)
- Break-through of mother nuclide
- Peptide quantification, identification of impurities
- Residual solvents from synthesis process

Part IV: Facilities

- Production in Hot laboratories
- Aseptic working techniques to be respected
- Radiopharmaceuticals have to be prepared in a class A environment
 - Shielded Laminar Flow Hood
 - Hot Cell
- If the radiopharmaceuticals are produced by in-house 'fabrications (ex. synthesis), the room of the preparation needs to be classified microbiologically → *GMP Laboratories!*

Small Scale Radiopharmacies

(KIT and ready to use therapeutique preparations)

- Personnel trained in aseptic working and radiation protection
- Ideally dedicated room for production
- Shielded Laminar Flow Hood, Class A



Big Scale Radiopharmacies, University Hospitals (KITs, ready to use therapeutic preparations, in-house fabrication)

- Personnel trained in aseptic working and radiation protection
- Supervision of a radiopharmacist for fabrications
- Dedicated room for production, dedicated room for QC
- Hot cell Class A, environment class B, C or D
- **GMP certified by the authorities**



GMP: Good Manufacturing Practice

- Adequate premises, space, equipment and materials
- Appropriately qualified and trained personnel
- Clear definition of manufacturing processes
- Validation of critical steps in the process
- Validation of any significant changes to the process
- Approved instructions and procedures for production, quality control, product release, etc.
- Quality assurance and quality control independent of production
- Traceability of manufacture
- Examination of complaints and investigation of quality defects
-



Conclusions Facilities

- Relatively “simple” facilities for Kit and ready to use preparations
- Less exhaustive quality systems for Kit and ready to use preparations
- Small nuclear medicine departments do not have the means to offer in-house syntheses and fabrications
- Fabrications are mainly performed by industry or university hospitals with big nuclear medicine facilities
 - GMP facilities obligatory, certification by authorities, regular inspections take place.

Part V: Legislation for Radiopharmaceuticals

In Switzerland there exist two main legal authorities:

- Swissmedic
- Federal Office of Public Health

(For application of radiopharmaceuticals within clinical studies, the Swiss Ethic Committee needs to be informed as well and evaluates the request.)

Swissmedic

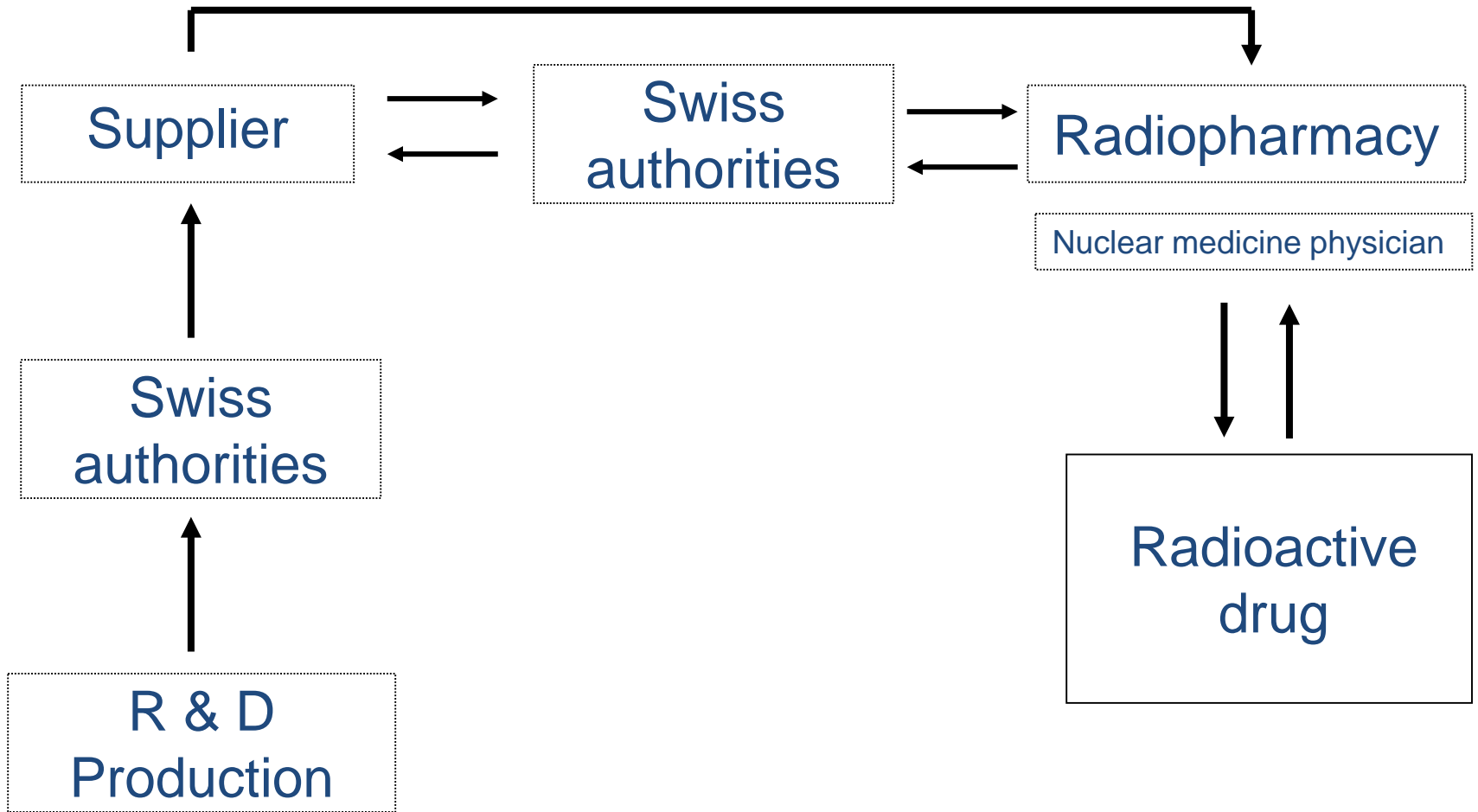
- Authorizations for importation of radiopharmaceuticals
- Authorizations for clinical studies
- Authorization of fabrication (in-house fabrication radiopharmaceuticals)
- GMP (Good Manufacturing Practice) inspections
- Quality System inspections
- Registrations of radiopharmaceuticals in Switzerland

Federal Office of Public Health

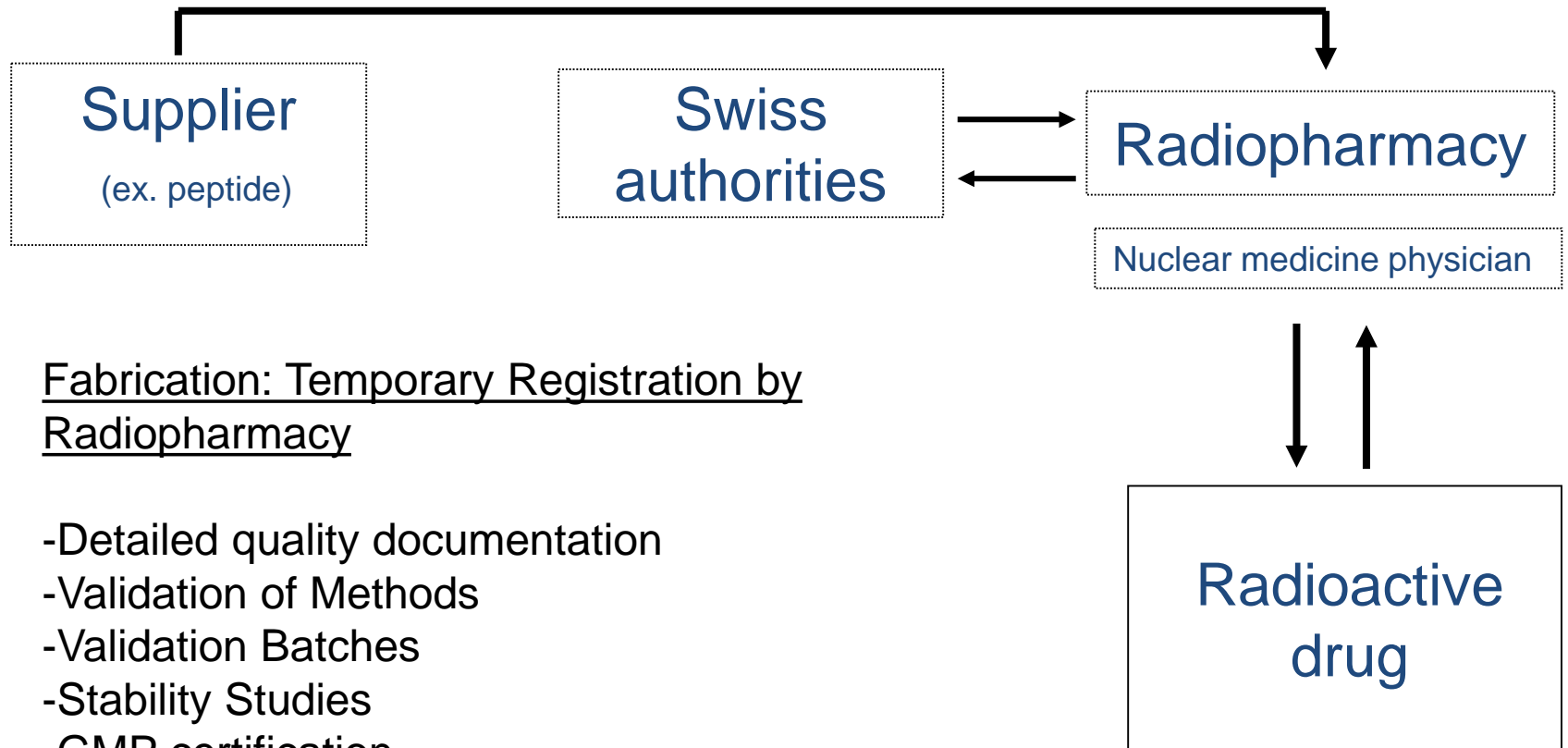
- All requests on (new) radiopharmaceuticals are approved by the FOPH for radioprotection aspects.
- Authorization radioactive substances (manipulation and administration)
- Conformity of controlled zones (radioprotection)
- Radioprotection/Dosimetry
- Guidelines for KIT preparations
- Quality assurance of activity measurements

→ Strong collaboration between Swissmedic and the FOPH concerning radiopharmaceuticals and their applications.

Commercialisation of Radiopharmaceuticals



In-house Production of Radiopharmaceuticals



Fabrication: Temporary Registration by Radiopharmacy

- Detailed quality documentation
- Validation of Methods
- Validation Batches
- Stability Studies
- GMP certification
- etc...

Guidelines and legal documents...

- Legal notices and textes from FOPH and Swissmedic
- European Pharmacopoeia → *individual monographs per product*
- Swiss Pharmacopoeia
- GMP Guidelines (PIC/S)

814.501

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Radiological Protection Ordinance

814.554

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Verordnung über den Umgang mit offenen radioaktiven Strahlenquellen

812.21

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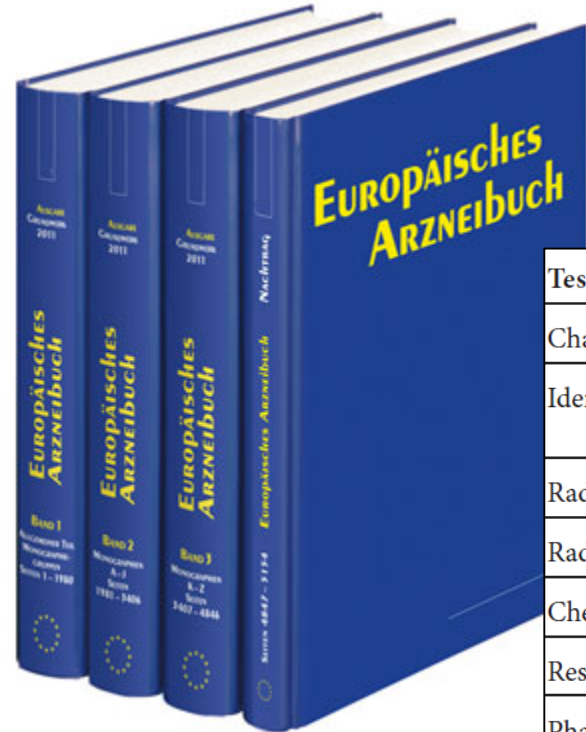
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Federal Act on Medicinal Products and Medical Devices

(Therapeutic Products Act, TPA)



Individual monographs for each radiopharmaceuticals



Test or parameter	Equipment and/or method
Characters, appearance	Visual inspection
Identity of radionuclide	Half-life determination; alpha-particle spectrometry; beta-particle spectrometry; gamma-ray spectrometry
Radiochemical identity	Liquid chromatography, thin-layer chromatography
Radiochemical purity	Liquid chromatography, thin-layer chromatography
Chemical purity	Liquid chromatography, thin-layer chromatography
Residual solvents	Gas chromatography
Pharmaceutical or physiological parameters	pH, osmolality
Microbiological parameters	Bacterial endotoxins, sterility
Radionuclidic purity	Half-life determination; gamma-ray spectrometry
Radioactivity content, concentration	Ionisation chamber
Specific radioactivity	Liquid chromatography, ionisation chamber
Enantiomeric purity	Chiral chromatography

...Radionuclide production → Starting materials → Radiopharmaceutical → QC → Packaging → Release...

Conclusions Legislation

- Swissmedic checks the radiopharmaceutical quality aspects and compliancy of radiopharmaceutical production with GPM normes.
- The FOPH checks for radiation safety and quality assurance of the productions (ex. qualification of radioactivity measurement instruments, infrastructure, etc...). The FOPH checks the compliancy of quality aspects in small scale radiopharmacies.
- Regular inspections by the FOPH take place in small scale and big scale radiopharmacies.
- Inspections by Swissmedic are only performed in radiopharmacies having an authorization for in-house fabrications (mainly industry and university hospitals). Small scale radiopharmacies with Kit and ready-to-use preparations are so far not inspected regularly by Swissmedic. The laws and guidelines of Swissmedic have to be applied though.

Part VI: Quality Control Methods

- TLC and paper chromatography (radiochemical purity)
- HPLC (identification, radiochemical purity, quantification)
- GC (residual solvents)
- Detection and measurement of radioactivity

Where do you find the information for the QC...

- SPC (Summary of Product Characteristics) of KITs and other radiopharmaceuticals.
- PhEur Monographies
- Legal Notices FOPH/Swissmedic
- Publications/Literature

Most QC methods are based on paper or thin layer chromatography. For in-house fabrications, HPLC and GC methods are used additionally.

Primary Quality Control Parameters

- Radionuclide purity
- Radionuclide identity (by gamma spectrometry)
- Amount of Radioactivity
- Chemical Purity
- Radiochemical Purity
- Sterility
- Apyrogenicity (endotoxines)
- pH Value
- Radionuclide identity
- Particle Size
-

Paper and Thin Layer Chromatography

- Analytical method used to separate substances.
- The mobile phase is a solution that travels up the stationary phase.
- The mobile phase is generally an alcohol solvent mixture, while the stationary phase is a strip of chromatography paper or an TLC stripe, the so called a chromatogram.

Retention factor (R_f)

- The ratio of the distance traveled by the substance to the distance traveled by the solvent.
- R_f values are usually expressed as a fraction of two decimal places.
- If R_f value of a solution is zero, the solute remains in the stationary phase and thus it is immobile.
- If R_f value = 1 then the solute has no affinity for the stationary phase and travels with the solvent front.

Retention factor (R_f)

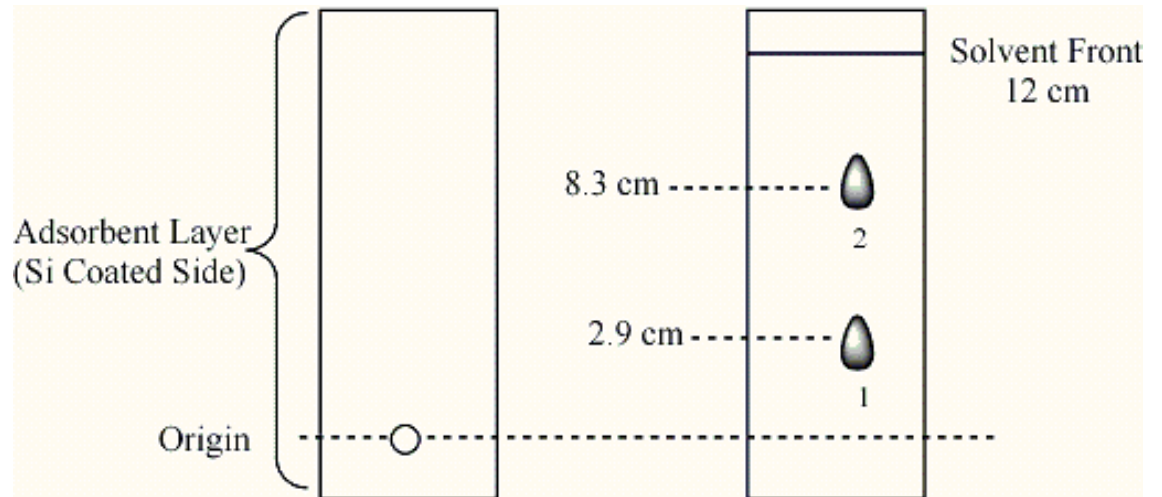
To calculate the R_f value, take the distance traveled by the substance divided by the distance traveled by the solvent (as mentioned earlier in terms of ratios).

Example:

- A compound travels 9.9 cm
- The solvent front travels 12.7 cm

➤ $R_f \text{ value} = (9.9/12.7) = 0.78$

The R_f value depends on temperature and the solvent used in, so several solvents offer several R_f values for the same substance.



$R_f = \text{Distance Traveled by Spot} / \text{Distance Traveled by Solvent}$

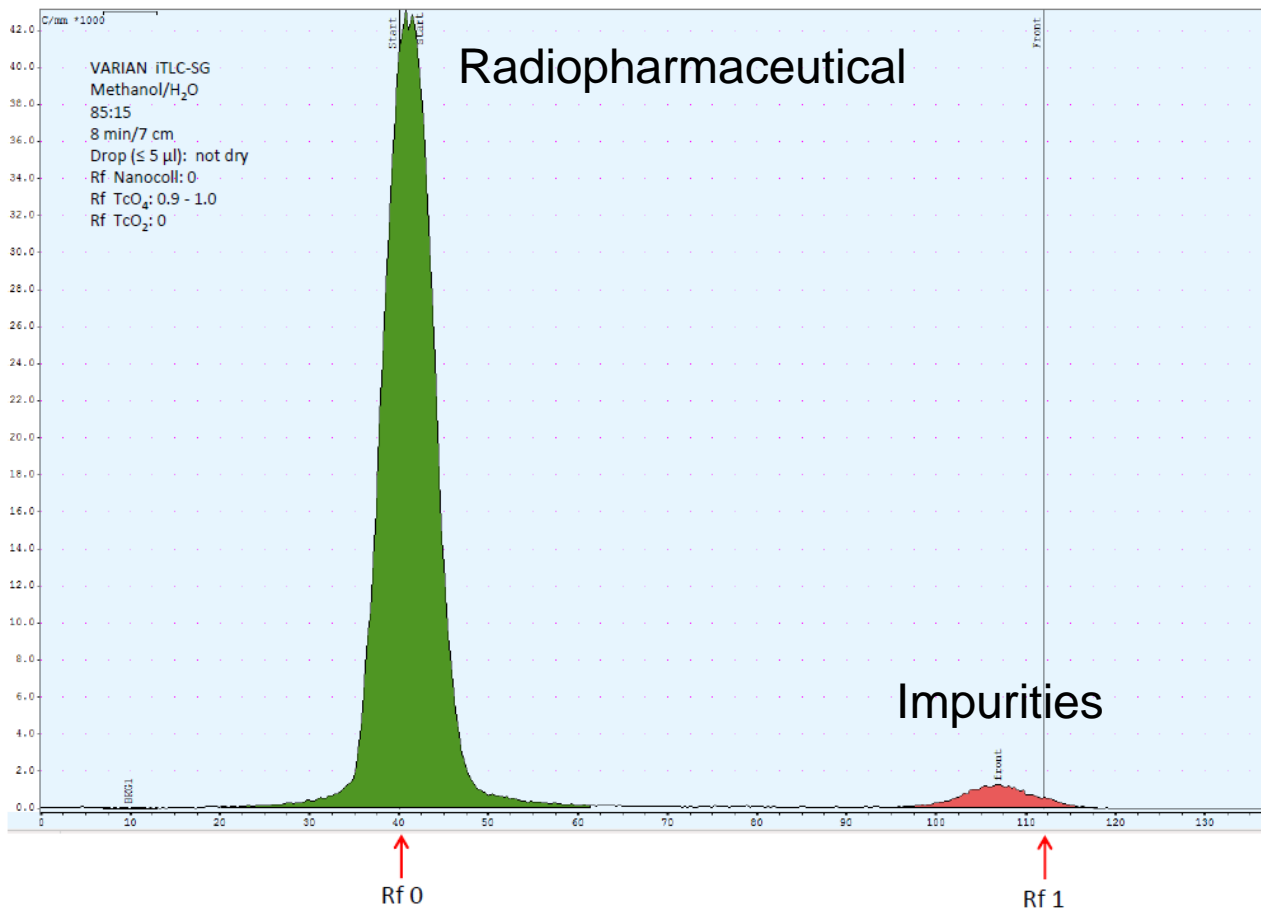
$$R_f(1) = 2.9 \text{ cm} / 12 \text{ cm} = 0.24$$

$$R_f(2) = 8.3 \text{ cm} / 12 \text{ cm} = 0.69$$

Note: R_f Values Are Always Less Than 1



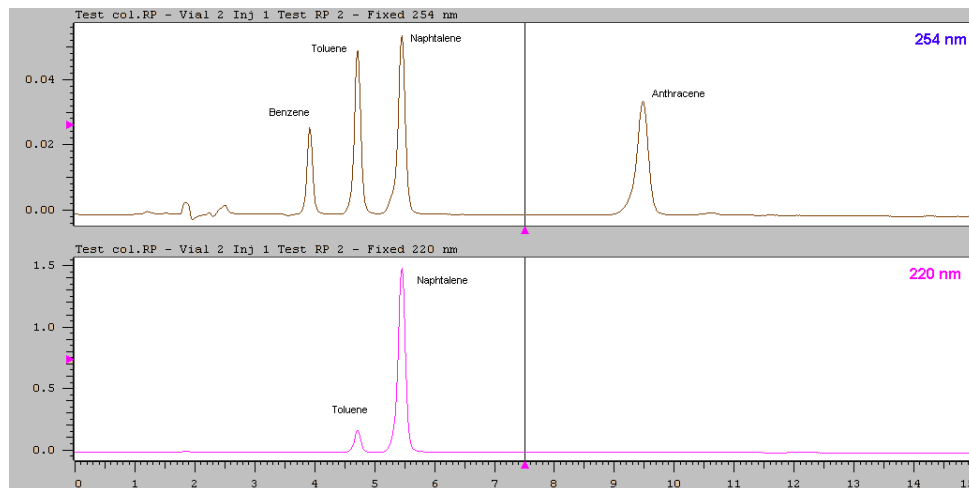
$$\% \text{ Impurity} = \frac{\text{Impurity}}{(\text{Impurity} + \text{Radioph.})} \times 100$$



HPLC quality control



A pressurized liquid solvent containing the sample mixture flows through a column filled with a solid adsorbent material which retains the individual components.



HPLC separates, identifies, and quantifies each component in a radiopharmaceutical.

- Module Radioactivity (labeled)
- Module UV-Visible (non labeled)

Gas Chromatography (GC)



Used for separating and analyzing compounds that can be vaporized without decomposition.

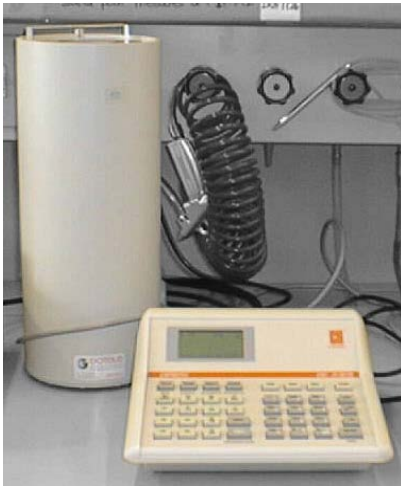
Used for testing the purity of a particular substance, or separating the different components of a mixture.

Relative amounts of such components can be determined.

- Quantification of residual solvents as ex. Ethanol or Acetone
- Physiological Effect of solvents, PhEur limits have to be respected

Dose Calibrator (activity measurement)

- Individual Radionuclides with specific calibration factor
- Geometry of measured sample is important



Capintec



*Intercomparaison
IRA*



Veenstra



NPL

Information on radiopharmaceuticals

- SPC (Summary of product characteristics)

<http://www.swissmedicinfo.ch/Accept.aspx?ReturnUrl=%2fdefault.aspx>