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 radiolabelling 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 ($^{99m}$Tc 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 \((^{99m}\text{Tc}\text{ Kit})\)

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

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

- Radionuclidic 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. $^{99m}$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 Molybdenum 99 break-through
- $^{68}$Ga generators: to be checked for Germanium 68 break-through
- Aluminium 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)

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 Radiopharmaciste (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 therapeutique preparations, in-house fabrication)

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

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**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
- Tracability 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

Supplier ↔ Swiss authorities ↔ Radiopharmacy

Swiss authorities

R & D Production

Nuclear medicine physician

Radioactive drug
In-house Production of Radiopharmaceuticals

- Supplier (ex. peptide)
- Swiss authorities
- Radiopharmacy

Fabrication: Temporary Registration by Radiopharmacy
- Detailed quality documentation
- Validation of Methods
- Validation Batches
- Stability Studies
- GMP certification
- etc...

Radioactive drug

Guidelines and legal documents...

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

Legal notices and texts from FOPH and Swissmedic
- European Pharmacopoeia → individual monographs per product
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- GMP Guidelines (PIC/S)
Individual monographs for each radiopharmaceuticals

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

Conclusions Legislation

- Swissmedic checks the radiopharmaceutical quality aspects and compliancy of radiopharmaceutical production with GPM norms.

- 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

- Radionuclidic purity
- Radionuclidic 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 (Rf)

- 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.

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

$$R_f \text{ value } = \frac{9.9}{12.7} = 0.779 \text{ or } 0.78$$

The $R_f$ value depends on temperature and the solvent used in, so several solvents offer several $R_f$ values for the same substance.
% Impurity = \frac{\text{Impurity}}{(\text{Impurity} + \text{Radioph.})} \times 100

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

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

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

Note: R_f \text{ Values Are Always Less Than 1}
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 item is important

![Images of Calibrators](Capintec, Intercomparaison IRA, Veenstra, NPL)

Information on radiopharmaceuticals

- SPC (Summary of product characteristics)