# EU Scientific Seminar 2019
# Developments in nuclear medicine – new radioisotopes in use and associated challenges

## Production of radiopharmaceuticals – regulatory issues

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# The Evolution of a Novel Radiopharmaceutical

„Cold“ chemistry / Design of target molecules/structures

Radionuclide production

Radiochemistry

Biological evaluation

Preclinical Phase

Radiopharmacy GMP

Clinical trial(s)

Phase 0

Phase 1

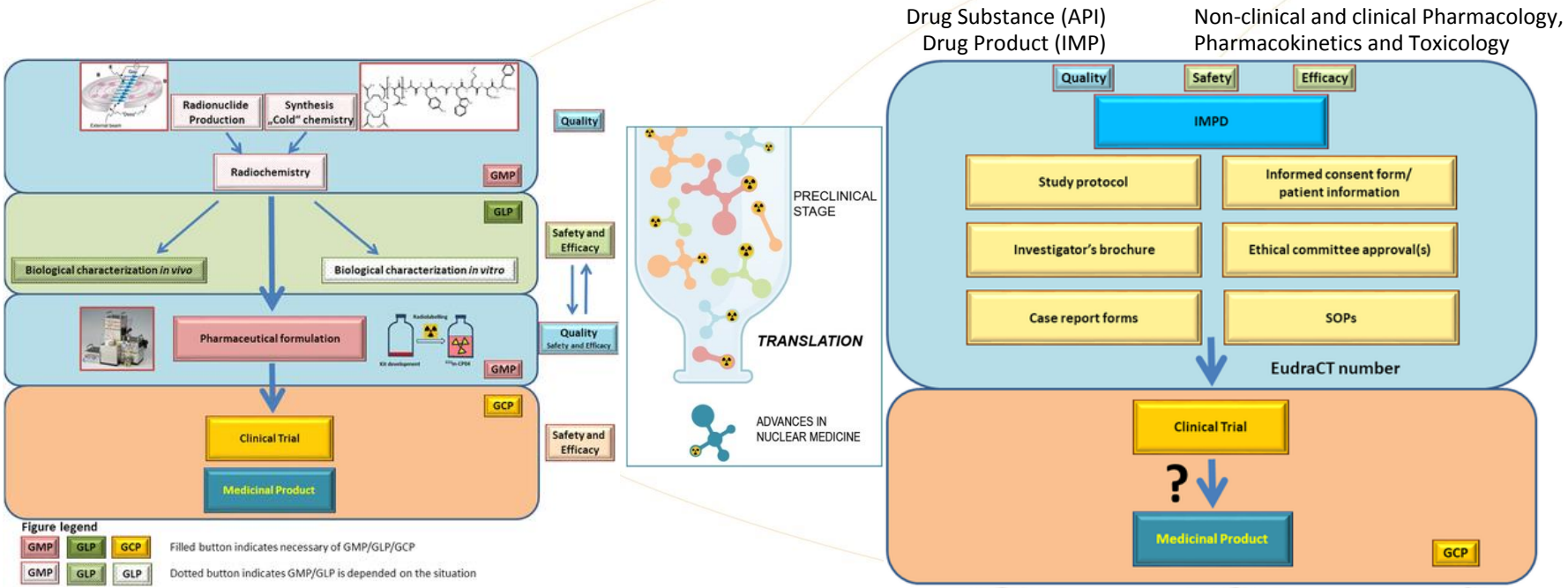
Phase 2

Phase 3

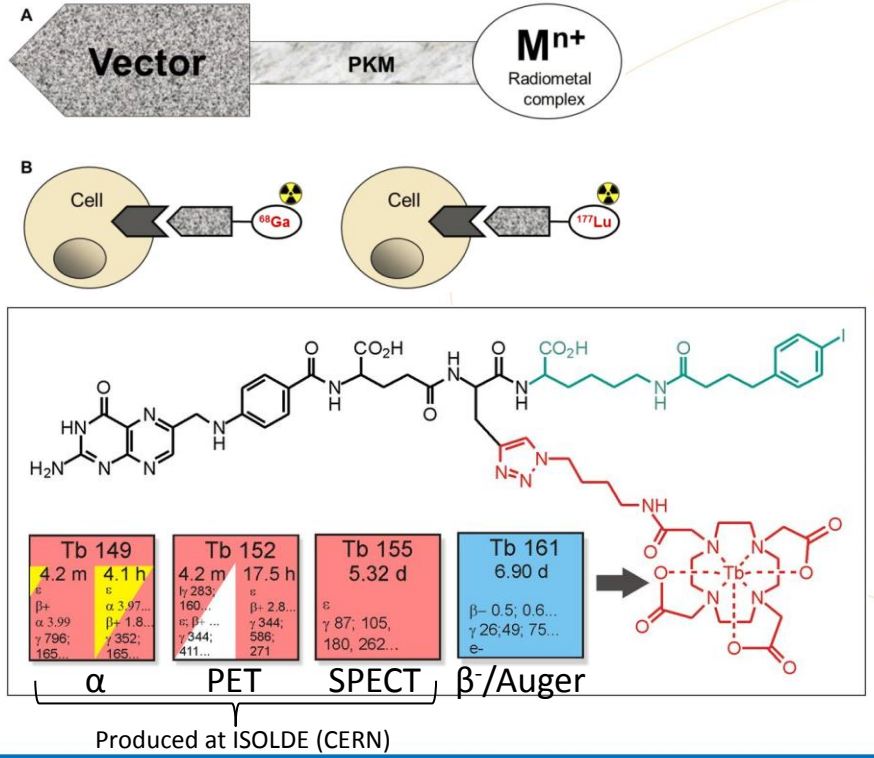
Marketing authorization

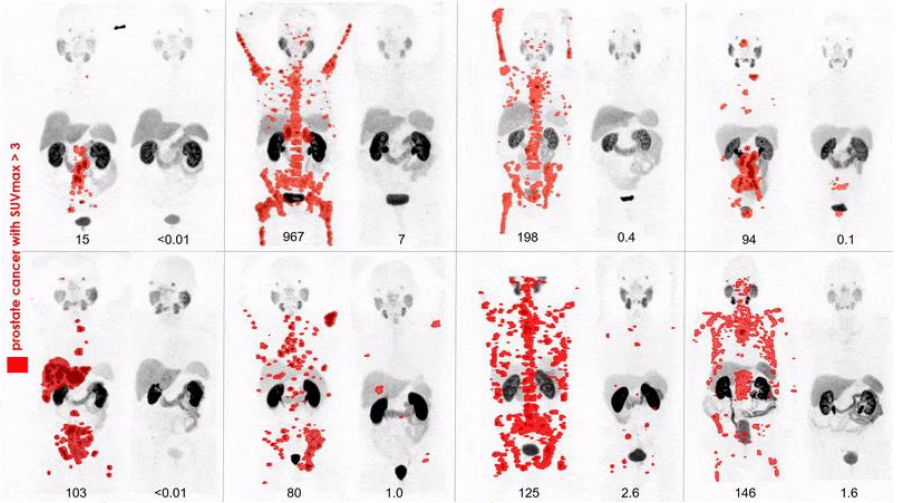
Phase 4

# The Clinical Translation of a Radiopharmaceutical



# The Theranostics principle




PSMA PET before and after Lutetium-177 PSMA-617 theranostic in 8 patients with metastatic prostate cancer who exhausted standard therapeutic options.

*Velikyan, Theranostics 2014*
*Müller et al., J Nucl Med 2012*

*Hofman et al., J Nucl Med 2018*

# Regulatory basis for the use of radiopharmaceuticals

| **Marketing authorization** | **Clinical trials** | **Extemporaneous preparations / Compounding in house** |
|---|---|---|
| European Pharmacopoeia (Ph. Eur.) General Monographs / Specific Monographs | | |
| Directive 2001/83/EC<br>Directive 2003/94/EC<br>Directive 2004/27/EC | Directive 2001/20/EC<br>Directive 2003/94/EC<br>Directive 2005/28/EC<br>Regulation 536/2014 | National competence |
| GMP Annex 3<br>EMA Guideline on Radiopharmaceuticals | GMP Annex 13<br>EC Guidance IMP/NIMP<br>EMA Guideline IMPD<br>EMA Guideline first-in-human ct | Ph. Eur. General Chapter 5.19<br>PIC/S GPP 010-4 incl. Annex 3<br>EANM guidelines/guidance<br>National guidance documents |

*Lange et al., Nucl Med Comm 2015*

# Regulatory basis for the use of radiopharmaceuticals

**Marketing authorization**

**Directive 2001/83/EC** (on the Community code relating to **medicinal products** for human use)
**Directive 2003/94/EC** (laying down the principles and guidelines of **good manufacturing practice** in respect of medicinal products for human use and investigational medicinal products for human use)
**Directive 2004/27/EC** (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use)

# Directive 2001/83/EC

**Impact for radiopharmaceuticals:**

- *Definitions*:
  - *Medicinal product*: (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.
  - *Radiopharmaceutical*: Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.
  - *Radionuclide generator*: Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.
  - *Kit*: Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.
  - *Radionuclide precursor*: Any other radionuclide produced for the radio-labelling of another substance prior to administration.

# Directive 2001/83/EC

**Impact for radiopharmaceuticals:**

- *Article 2*:
  - 1. This Directive shall apply to *medicinal products for human use intended to be placed on the market* in Member States and either prepared industrially or manufactured by a method involving an industrial process.
- *Article 3*:
  - This Directive shall not apply to:
  - 1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).
  - 2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).

# Directive 2001/83/EC

**Impact for radiopharmaceuticals:**

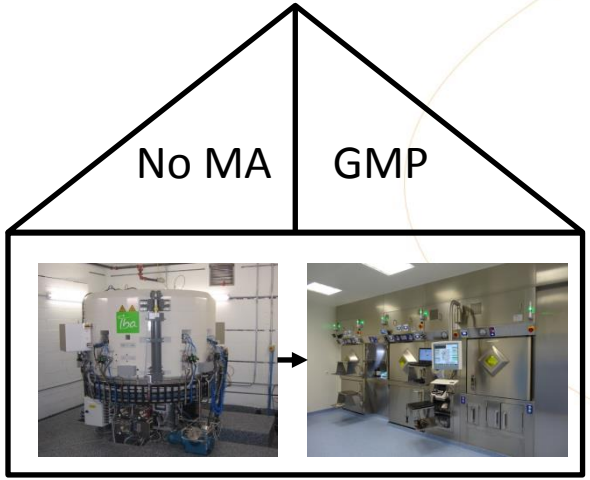
- Marketing authorization
- *Article 6*:
  - 1. No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive…
  - 2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, kits, **radionuclide precursor radiopharmaceuticals** and industrially prepared radiopharmaceuticals.

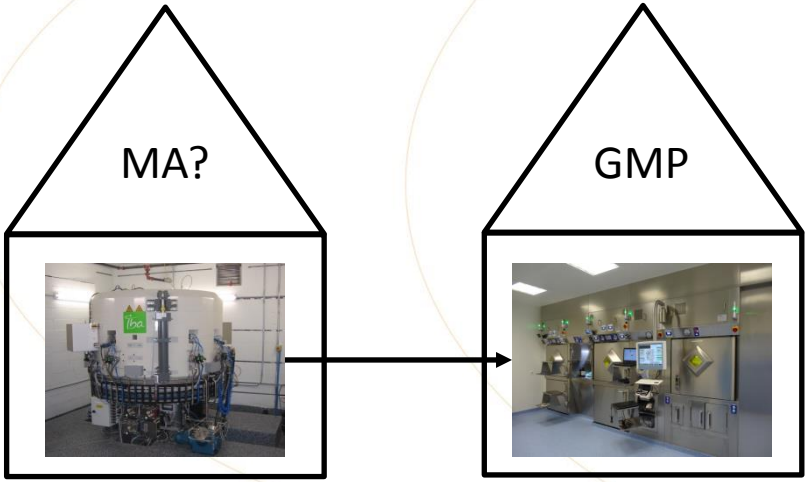
*Def.: Radionuclide precursor*: Any other radionuclide produced for the radio-labelling of another substance prior to administration. → Radiometals for theranostic applications but also F-18 or C-11?

*Def.: Radiopharmaceutical*: Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose. → e.g. F-18 FDG

Def.: Radionuclide precursor **radiopharmaceutical**? → Not defined in Directive 2001/83/EC!

# Directive 2001/83/EC: how to interpretate article 6 paragraph 2?



# Directive 2001/83/EC

A MA for the radionuclide (precursor) is required when it is produced at an external site and placed on the market.

A MA for the radionuclide (precursor) is not required when it is produced on-site and not placed on the market.

Propose to clarify the definition of „radionuclide precursor“ within directive 2001/83/EC:

Radionuclide precursor ***radiopharmaceutical***: a licensed radionuclide precursor that that can be added to a licensed kit for radiopharmaceutical preparations.

Radionuclide precursor ***starting material***: a radionuclide precursor that is to be used in a radiochemical synthesis that is followed by one or more purification steps.

# Regulatory basis for the use of radiopharmaceuticals

**Clinical trials**

**Directive 2001/20/EC** (on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of **good clinical practice** in the conduct of **clinical trials** on medicinal products for human use)
**Directive 2003/94/EC** (laying down the principles and guidelines of **good manufacturing practice** in respect of medicinal products for human use and investigational medicinal products for human use)
**Directive 2005/28/EC** (laying down principles and detailed guidelines for **good clinical practice** as regards **investigational medicinal products** for human use, as well as the requirements for authorisation of the manufacturing or importation of such products)
**Regulation 536/2014** (on clinical trials on medicinal products for human use, and **repealing Directive 2001/20/EC**)

*Lange et al., Nucl Med Comm 2015*

# Regulation 536/2014

**Clinical trials**

**Regulation 536/2014** (on clinical trials on medicinal products for human use, and **repealing Directive 2001/20/EC**)

Key features:

- More harmonization in the submission process, transparency and higher safety standards of clinical trials
- Into force since 16th April 2014
- Entry into application depends on delivery and audit of a centralized and harmonized clinical trials portal and database by EMA (postponed until 2020)
- (Electronic) application for clinical trials will change from National to European level

# Regulation 536/2014

Impact for radiopharmaceuticals:

- *Article 61 (Authorisation of manufacturing and import)*
  - 1. The manufacturing and import of investigational medicinal Products in the Union shall be subject to the holding of an authorisation.
  - 5. Paragraph 1 shall **not** apply to any of the following processes:
    - (b) preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;
  - 6. Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections.

# Regulation 536/2014

Impact for radiopharmaceuticals:

- *Article 63 (Manufacturing and import)*
  - 1. Investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ('good manufacturing practice'). …
  - 2. Paragraph 1 shall not apply to the processes referred to in Article 61(5).

**YES or maybe or maybe not**
Article 61(6)
→ Member states shall decide on requirements

Good Manufacturing Practice for RP used as diagnostic IMP:
***Yes or No?***

**NO**
Article 63(2)
→ ref. Article 61(5)

Therapeutic radiopharmaceuticals?

# Summary

A clear clarification or re-definition of the terms *radionuclide precursor* and *radionuclide precursor radiopharmaceutical* is necessary within directive 2001/83/EC to assure the production and the availability for patient care of e.g. novel F-18 based radiopharmaceuticals at centers/hospitals without on-site cyclotron.

Regulation 536/2014 has not come into applicaton for several years and is lacking substantial information on therapeutic radiopharmaceuticals.