

# Presentation of the guidance and posology framework relevant to therapeutic radiopharmaceuticals

**Vanessa Fradin-Da Ros**

Product Lead

Oncology and Radiopharmaceuticals Human Medicines Division





EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH



## EMA is

- **A decentralised agency of the EU**
- **Responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU**
- **A networking organisation** whose activities involve thousands of experts from across Europe carrying out the work of EMA's scientific committees

# EMA protects human & animal health

- Facilitate **development and access to medicines**
- **Evaluate applications for marketing authorisation**
  - 7 Scientific committees providing independent recommendations on medicines based on a comprehensive scientific evaluation of data
  - Centralised procedure
  - EMA referral procedures
  - Coordination of inspections
- **Monitor the safety** of medicines across their life cycle
- **Provide reliable information** on human and veterinary **medicines** in lay language

# EMA does not



Evaluate all marketing authorisation applications (MAAs) of all medicines in the EU



Evaluate clinical trials applications (CTAs)



Develop treatment guidelines



Provide medical advice



Develop laws concerning medicines



Issue marketing authorisation (MA)




...


# Stakeholder Engagement

- To optimise the Agency's public service role in improving human and animal health, **EMA systematically integrates multi-stakeholder engagement** by design into its key activities and strategic priorities
- EMA engages with stakeholders to:
  - ensure that EMA decisions are well informed, meet stakeholders' needs and reach them
  - harness the widest expertise available
  - raise awareness and understanding of EMA's evolving role and its work
  - reinforce confidence and trust in the scientific and regulatory outcomes and in the EU system


# A few principles




The summary of product characteristics (SmPC) is the basis of information for healthcare professionals (HCPs) on how to use the medicine safely and effectively.



The therapeutic indication reflect in which disease/condition and target population the benefit / risk (B/R) balance is established to be positive, before presenting other conditions for use and presenting information on benefits (5.1) or risks (4.3, 4.4, 4.8 and others).



The European public assessment report (EPAR)) presents the B/R assessment of the medicine itself. Apart from the B/R presented in the EPAR, there is the relative B/R assessment (vs other products, mainly under remit of HTA bodies) and the B/R assessment at individual level.



PI provides HCPs and Patients with conditions for use of the product in the approved indication together with information on benefits and risks (based on relevant data submitted by the applicant / MAH to support the MA) to support therapeutic choice and safe and effective use at individual level.

# Product-information (PI) requirements: EMA guidance

- Practical advice on how to draw up the PI for human medicines (incl. summary of product characteristics (SmPC), labelling and package leaflet (PL)).
- Explains the content + standard headings + the most commonly used standard statements and terms in all official EU languages + Icelandic & Norwegian AND defines the format and layout for the [product information](#).
- EMA's guidance is without prejudice to:
  - any final positions from the Agency, the [CHMP](#) or European institutions relating to the contents of the documents;
  - the binding nature of the relevant legislation;
  - any legal interpretations given by the EC or the CJ of the EU.

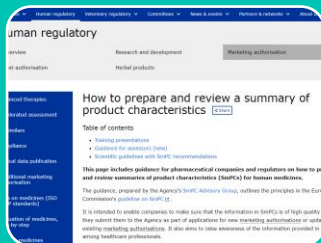
# Guideline on SmPC / posology



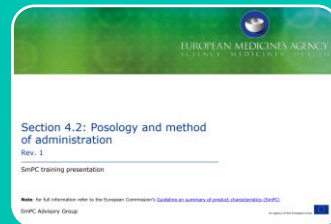
EudraLex

Volume 2C: Regulatory guidelines

Guideline on SmPC Rev.2



How to prepare and review a summary of product characteristics: here



SmPC training presentation: Section 4.2: Posology and method of administration



# NTA vol 2C, A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) September 2009

---

## Introduction :

- Principles applicable to all medicinal products.
- Depend on the scientific knowledge on the medicinal product, the legal basis of a marketing authorisation and public health needs.
- Deviation should therefore be justified in the relevant Overview or Summary in the MAA.

# NTA vol 2C, A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) September 2009

- Specific requirements for radiopharmaceuticals in terms of :
  - **DOSIMETRY** (section 11): Full details of internal radiation dosimetry to be included.
  - **INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS** (section 12): additional detailed instructions for extemporaneous preparation and QC + where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform to its specifications. Special instructions relating to the disposal of containers and unused contents should also be included.

# Guideline on SmPC / posology

Scientific guidelines with SmPC recommendations

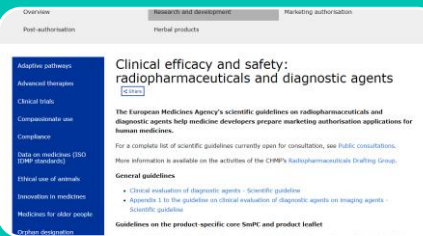
Table of contents

<b>Table of contents</b> .....	<b>1</b>
<b>1. Clinical efficacy and safety</b> .....	<b>1</b>
<b>2. Quality and biological</b> .....	<b>4</b>
<b>3. Non-clinical</b> .....	<b>5</b>

Note: the tables below only include adopted scientific guidelines which refer specifically to the SmPC.  
For complete information on scientific guidelines, please refer to the European Medicines Agency.

Scientific guidelines with SmPC recommendations –  
Radiopharmaceuticals - [EMA/813125/2012 rev. 6](#)

Under  
revision



Overview

Post authorization

Research and development

Marketing authorization

Medical products

Adoptive pathways

Advanced therapies

Clinical trials

Complementary use

Compliance

Data on medicines (DDI / DR / interactions)

Off-label use of animals

Innovation in medicines

Medicines for older people

Orphan designation

**Clinical efficacy and safety: radiopharmaceuticals and diagnostic agents**

[Clinical](#)

The European Medicines Agency's scientific guidelines on radiopharmaceuticals and diagnostic agents help medicine developers prepare marketing authorisation applications for human medicines.

For a complete list of scientific guidelines currently open for consultation, see [Public consultations](#).  
More information is available on the activities of the CHMP's Radiopharmaceuticals Drafting Group.

**General guidelines**

- [Clinical evaluation of diagnostic agents - Scientific guideline](#)
- [Appendix 1 to the guideline on clinical evaluation of diagnostic agents on imaging agents - Scientific guideline](#)

[Guidelines on the product-specific core SmPC and product leaflet](#)

EMA webpage on [Clinical efficacy and safety: radiopharmaceuticals and diagnostic agents](#)

Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals

Draft Agreed by Radiopharmaceuticals drafting group	February 2011
Adoption by CHMP for release for consultation	17 March 2011
End of consultation (deadline for comments)	25 April 2011
Adoption by CHMP	23 September 2011

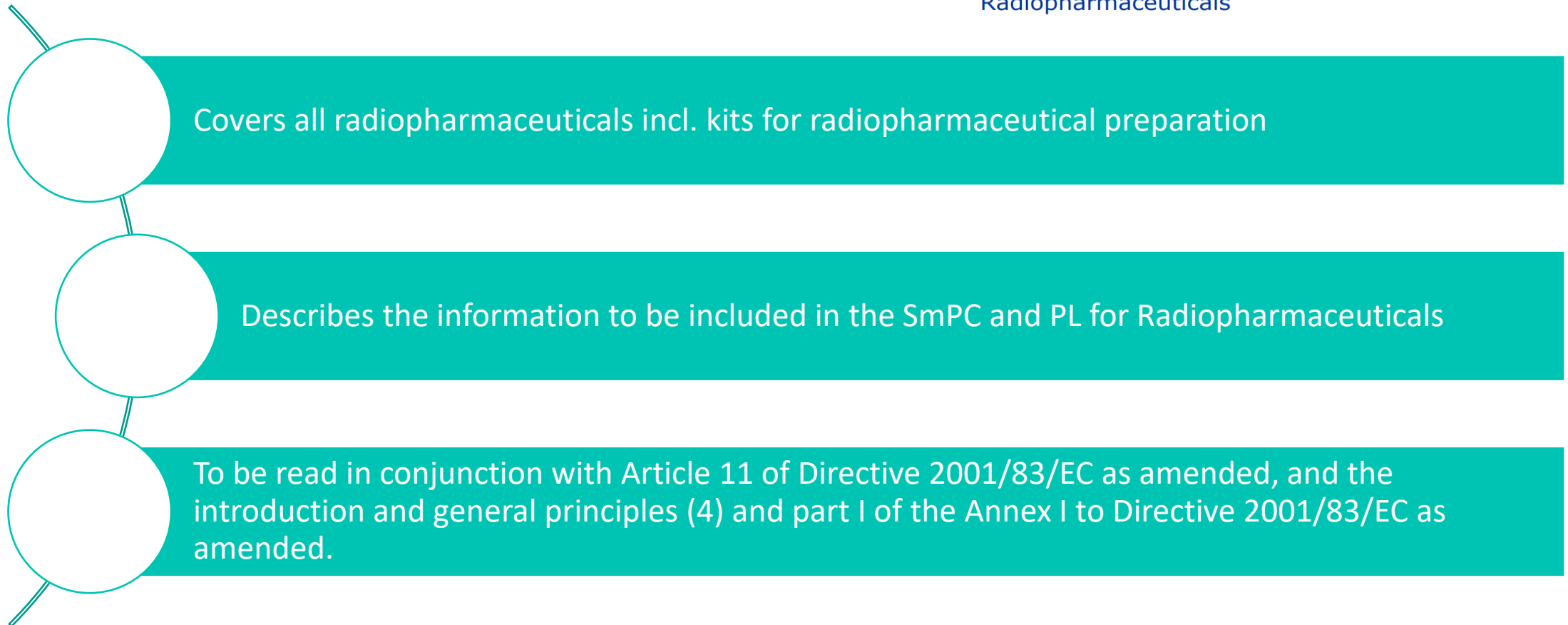
This guideline (EMA/CHMP/167834/2011) replaces the core SmPC for Radiopharmaceuticals

Guideline on core SmPC and Package Leaflet for  
Radiopharmaceuticals - [EMA/CHMP/167834/2011](#)

# Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals

23 September 2011  
EMA/CHMP/167834/2011  
Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals



# Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals

- 4.2 Posology and method of administration

## Posology

<Adults>

*[Posology should as a general rule*

*- state a suggested activity range*

*- be based on a patient of average weight (70 kg).*

*The activity range should be stated in MBq in round numbers. A statement that “other activities may be justifiable” may also be considered appropriate.*

*Reference to European procedural guidelines should be made if required.]*

# Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals

Renal impairment / Hepatic impairment

<Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.>

Paediatric population

*[Paediatric dosing regimens, when applicable, should be clearly stated when an indication exists in this subgroup. If there are data available which are not sufficient to support an indication in the paediatric population, these data may be summarised in section 5.1 of the SmPC with a cross reference from section 4.2, Paediatric population. Reference could be made to relevant data proposed by bodies specialised in radiation protection and/or nuclear medicine.]*

*<The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activities to be administered to children and to adolescents may be calculated according to [include here relevant data proposed by bodies specialised in radiation protection and/or nuclear medicine]. >*

[When the minimum recommended activity in the EANM dosage card for paediatrics is different than the baseline activity, it should be stated here.]

# Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals

## Method of administration

*[Product specific, it should be specified if multidose or for single use only.]*

*[For kits for radiopharmaceutical preparation:]* <This medicinal product should be reconstituted before administration to the patient.>

<For instructions on <reconstitution> <dilution> <extemporary preparation> of the medicinal product before administration, see section <12>.>

<For patient preparation, see section 4.4.>

*[For a diagnostic radiopharmaceutical intended for imaging or for a therapeutic radiopharmaceutical allowing imaging biodistribution]*

<Image acquisition>

*[General recommendations should be given about the recommended (minimal) number of imaging times, the delay between administration and imaging, some particular types of acquisition that are recommended in all or some of the indicated clinical settings, such as tomoscintigraphy SPECT, dynamic acquisition (rapid change of biodistribution over time), fusion with another imaging modality ... ]*

# Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals

- 4.4 Specials warnings and precautions for use  
(...)

## Individual benefit/risk justification

*[The as low as reasonably achievable (ALARA) statement should be included in every radiopharmaceutical:]* **For each patient, the radiation exposure must be justifiable by the likely benefit.**

The activity administered should in every case be as low as reasonably achievable to obtain the required <diagnostic information>  
<therapeutic effect>.



# Therapeutic RPs (V10) authorised centrally (CAPs)

CAP	Indication high level summary
<b>Quadramet</b> (samarium SM-153 lexidronam pentasodium)	bone pain
<b>Zevalin</b> (ibritumomab tiuxetan)	NHL & follicular lymphoma
<b>Yttriga</b> (yttrium ( <sup>90</sup> Y) chloride)	radiolabelling of carrier molecules
<b>Xofigo</b> (radium-223)	castration-resistant prostate cancer
<b>Lumark</b> (lutetium ( <sup>177</sup> Lu) chloride)	radiolabelling of carrier molecules
<b>EndolucinBeta</b> (lutetium ( <sup>177</sup> Lu) chloride)	radiolabelling of carrier molecules
<b>LUTATHERA</b> (lutetium ( <sup>177</sup> Lu) oxodotreotide)	Gastro-entero-pancreatic neuroendocrine tumors
<b>Pluvicto</b> (lutetium ( <sup>177</sup> Lu) vipivotide tetraxetan)	PSMA+ metastatic castration resistant prostate cancer
<b>Lutetium (<sup>177</sup>Lu) chloride Billev</b> (lutetium ( <sup>177</sup> Lu) chloride)	radiolabelling of carrier molecules

# Lumark (lutetium ( $^{177}\text{Lu}$ ) chloride) 80Gbp/ml

- **4.2 Posology and method of administration**

Lumark is only to be used by specialists experienced with *in vitro* radiolabelling.

### Posology

The quantity of Lumark required for radiolabelling and the quantity of the medicinal product to be radiolabelled with lutetium( $^{177}\text{Lu}$ ) that is subsequently administered will depend on the medicinal product to be radiolabelled and its intended use. Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.  
(...)

# Lumark

(lutetium ( $^{177}\text{Lu}$ )  
chloride)  
80Gbp/ml

- **4.4 Special warnings and precautions for use**

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect. Lumark is not to be administered directly to the patient but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates. (...)

# Lutathera

(lutetium ( $^{177}\text{Lu}$ )  
oxodotreotide)

- **4.2 Posology and method of administration**

Lutathera should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6) and after evaluation of the patient by a qualified physician.

### Posology

#### Adults

The recommended treatment regimen of Lutathera in adults consists of 4 infusions of 7 400 MBq each. The recommended interval between each administration is 8 weeks ( $\pm 1$  week). Information on dose modifications to manage severe or intolerable adverse drug reactions is given in the respective section

# Lutathera

(lutetium ( $^{177}\text{Lu}$ )  
oxodotreotide)

- **4.4 Special warnings and precautions for use**

Individual benefit-risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

Given the mechanism of action and the tolerance profile of Lutathera, it is not recommended to start treatment with Lutathera in patients with somatostatin receptor-negative or mixed visceral lesions according to somatostatin receptor imaging. (...)

# Pluvicto (lutetium ( $^{177}\text{Lu}$ ) vipivotide tetraxetan)

- **4.2 Posology and method of administration**

### Important safety instructions

Pluvicto should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6) and after evaluation of the patient by a qualified physician.

Radiopharmaceuticals, including Pluvicto, should be used by or under the control of healthcare professionals who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorised to license the use of radiopharmaceuticals.

### Patient identification

Patients should be identified for treatment by PSMA imaging.

### Posology

The recommended treatment regimen of Pluvicto is 7 400 MBq intravenously every 6 weeks ( $\pm 1$  week) for up to a total of 6 doses, unless there is disease progression or unacceptable toxicity.

Medical castration with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in patients not surgically castrated.

# Pluvicto

(lutetium ( $^{177}\text{Lu}$ )  
vipivotide  
tetraxetan)

- **4.4 Special warnings and precautions for use**

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.(...)

# Lutetium (<sup>177</sup>Lu) chloride Billev (lutetium (<sup>177</sup>Lu) chloride)

- **4.2 Posology and method of administration**

Lutetium (<sup>177</sup>Lu) chloride Billev is only to be used by specialists experienced with *in vitro* radiolabelling.

### Posology

The quantity of Lutetium (<sup>177</sup>Lu) chloride Billev required for radiolabelling and the quantity of lutetium (<sup>177</sup>Lu)-labelled medicinal product that is subsequently administered will depend on the medicinal product radiolabelled and its intended use. Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.  
(...)



# Lutetium (<sup>177</sup>Lu) chloride Billev (lutetium (<sup>177</sup>Lu) chloride)

- **4.4 Special warnings and precautions for use**

### Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

Lutetium (<sup>177</sup>Lu) chloride Billev is not to be administered directly to the patient but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides, vitamins or other substrates.

# Reminder on legal status of guidelines

Guidelines are to be considered as a **harmonised EU position** on how to **interpret and apply requirements** to demonstrate quality, safety and efficacy set out in the directives.

Guidelines are to be followed to facilitate development, assessment, approval and control of medicinal products in the EU.

Deviations must be duly justified in the dossier at the time MA submission.



# Radiopharmaceuticals focus group – Oncology European Specialised Expert Community (ESEC)

CHMP /  
ONCWP

- CHMP establishes a number of working parties (WP) at the beginning of each 3-year mandate. **Most WPs operate under the governance of a domain. These WPs have expertise in a particular scientific field and are composed of members selected from the list of European experts maintained by the Agency.**
- WPs can be supported by operational expert groups (OEGs), temporary drafting groups (tDGs) and European specialised expert communities (ESECs).

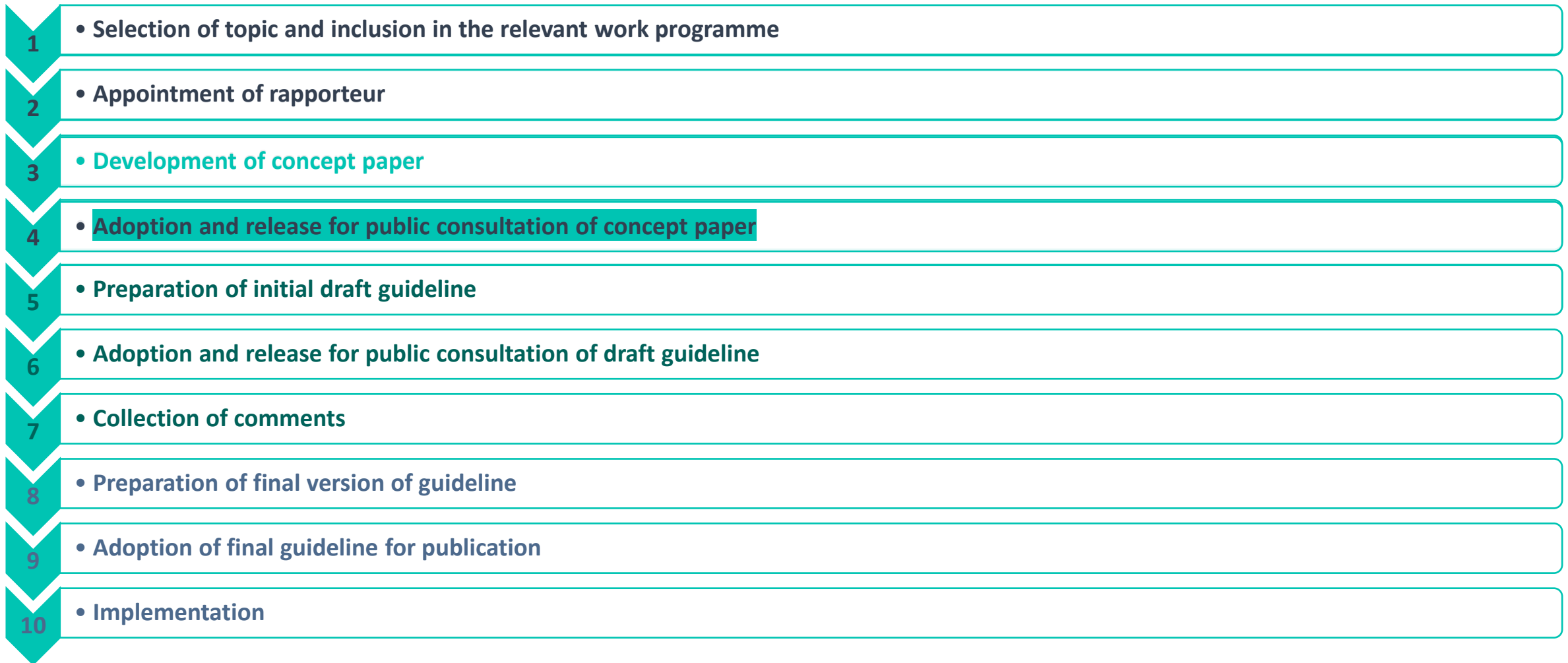
ONCWP /  
ESEC-O

- **Radiopharmaceuticals expertise is part of the Oncology ESEC supporting the ONCWP.**
  - ➔ Kick off meeting of the Radiopharmaceuticals focus group - Nov 2023.

tDG

- **WORK IN PROGRESS**(ONCWP workplan for 2024).
  - ➔ tDG set up to support development of a Concept paper on evaluation of therapeutic radiopharmaceuticals

# Procedure for EU guidelines and related documents within the pharmaceutical legislative framework, March 2009 (EMA/P/24143/2004 Rev. 1 corr):



# Concept paper development, adoption for consultation

- CP conveys the need for discussion of a specific issue but does not elaborate on the solutions
- Adopted for public consultation, usually 2-3 months
- Content is the basis for the future Guideline or Reflection Paper
- SIMPLERAD project conclusions to contribute to inform future regulatory discussions including when drafting the CP



# Conclusions



**Specificities of radiopharmaceuticals considered in relevant Guideline including posology.**



**PI: provides HCPs and Patients with conditions for use of the product in the approved indication together with information on benefits and risks (based on relevant data submitted by applicant / MAH to support the MA) to support therapeutic choice and safe and effective use at individual level.**



**Activities for the Radiopharmaceuticals DG were put on hold from 2019 till May 2023 (BCP)**



**Concept paper on evaluation of therapeutic RPs in oncology (ONCWP work plan for 2024)**



**Radiopharmaceuticals focus group belonging to Oncology European Specialised Expert Community ([ESEC](#)) restarted work in November 2023**

# Thank you