Radiolanthanides in the pharmaceutical regulatory framework in Europe

The PRISMAP Radiolanthanides Workshop

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27 EU PRISMAP Medical Radionuclides

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Radiolanthanides for a medicinal purpose= Medicinal Product (Directive 2001/83EC)

Medicinal product ("*Drug*"):

- 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**

Exemption:

A Radiolanthanide used in a sealed source for treatment (e.g. microspheres)

→ **Medical device**

Regulatory basis for the use of (Radio)Pharmaceuticals within the EU

Marketing Authorization

- Directive 2001/83/ EC ("Community Code on Medicinal Products", "Pharmaceutical Directive")

In revision

Clinical Trial

- Regulation EU No 536/2014 („Clinical Trials Regulation")

„New"

„Extemporaneous Preparation" , Compounding

- National legislation

Impacted by revision of Dir 2001/83

European Commission

PUBLIC HEALTH

European Commission > DG Health & Consumers > Public health > News and updates on pharmaceuticals > Eudralex

A radiopharmaceutical is?

Directive 2001/83/EC, Article 1

6. *Radiopharmaceutical:*

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

7. *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.

8. *Kit*

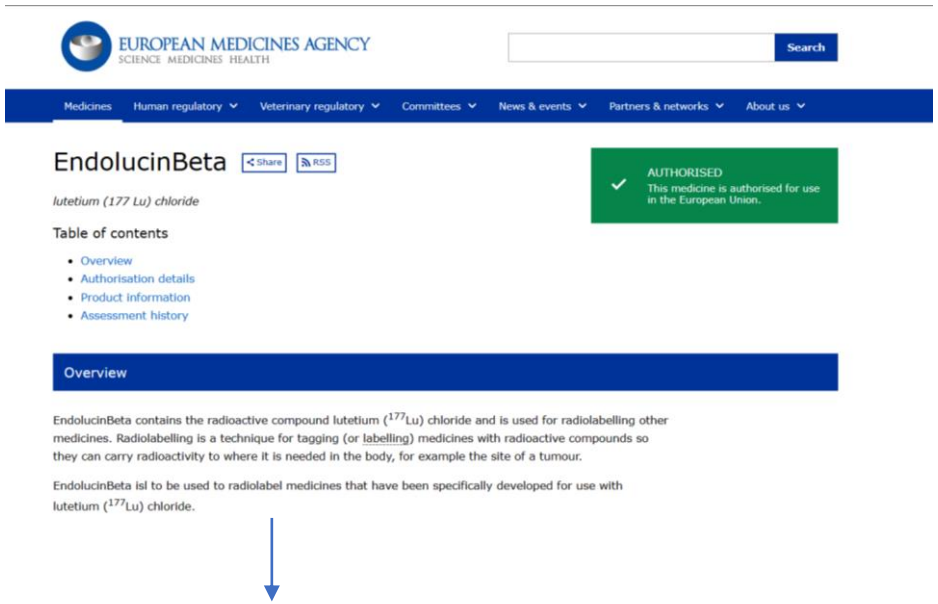
Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

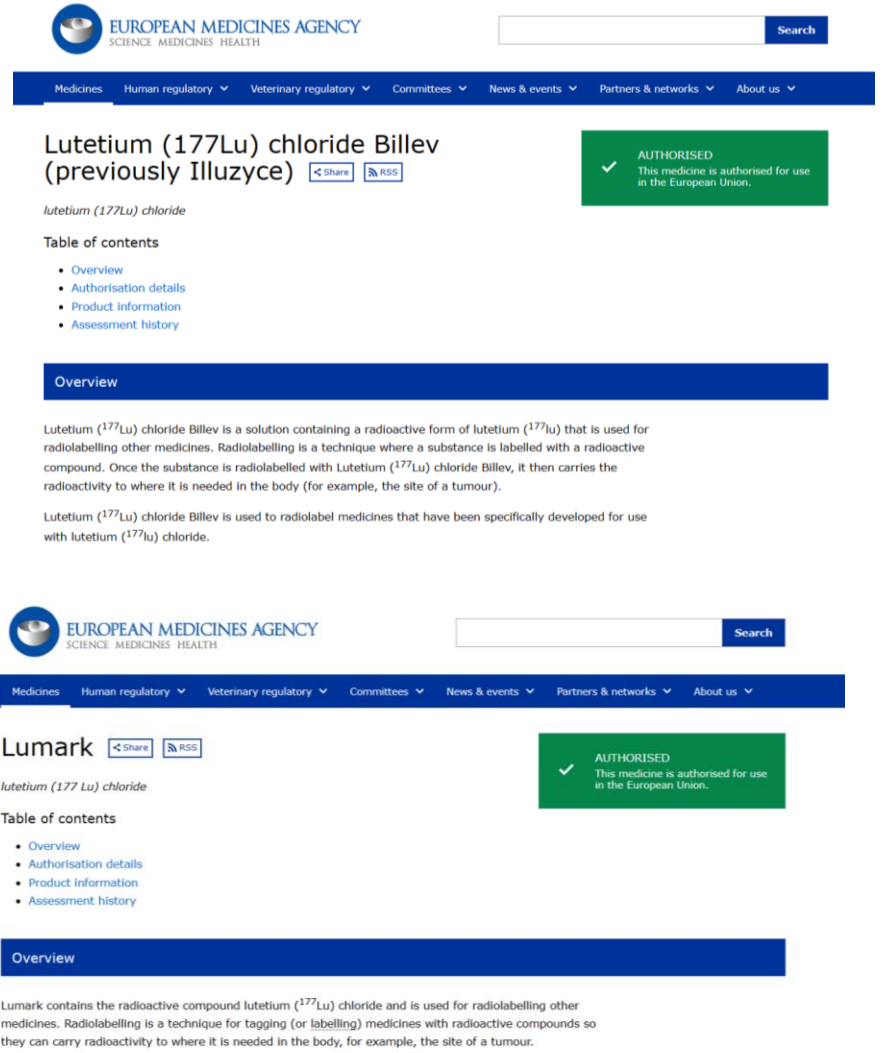
9. *Radionuclide precursor:*

Any other radionuclide produced for the radiolabelling of another substance prior to administration.

Legal Implications: Directive applies to all these products including requirement for **manufacturing authorisation** of the institution, licensing (**marketing authorization**), responsibilities, distribution, labelling……

Marketing Authorization requirement





SmPC: 4.1 Therapeutic indications: EndolucinBeta is a radiopharmaceutical precursor, and it is not intended for direct use in patients. It is to be used only **for the radiolabelling of carrier molecules** that have been specifically developed and **authorised** for radiolabelling with Lutetium (177Lu) chloride

→ So far no authorized „carrier molecule“ within the EU, only final products (Lutathera, Pluvicto)

Prismap

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Question to EMA (Innovation Task Force Meeting)

What are the experts' opinions (regulators) on the regulatory definition of a radionuclide used for preparation of an Investigational Medicinal Product intended to be applied in early phase clinical trials?
(*does my radionuclide require a marketing authorization*)

Answer:

A **radionuclide** supplied from a separate production site to a producer (and applicant) of an Investigational Medicinal Product **does not require** to have a **marketing authorization (MA), it can be considered as a starting material**.

However, the applicant`s IMPD must contain **sufficient information on the manufacturing process** to allow the competent authority **to judge the quality of the starting material (the radionuclide)** such as target material specifications, target preparation and irradiation parameters.

How to prepare radiolanthanides - Requirement for GMP?

Directive 2001/83/EC

- Article 40(f). Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. ….
- Art. 46 (f): .. need to comply with GMP for the preparation of **finished (radio)pharmaceuticals**
- … and for the preparation of **active substances**
- …
- …..and check for GMP production of excipients

- art. 47: it refers to the need for a specific «GMP» Directive (…….then the Dir. 2003/63/EC)

EudraLex Vol. 4, Annex 3: Manufacture of Radiopharmaceuticals, Introduction

3. (Applicability of GMP to manufacturing processes)

Type of manufacture	*Non - GMP **	*GMP part II & I*	
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	*Reactor/Cyclotron Production*	*Chemical synthesis*	*Purific steps*
Radionuclide Generators	*Reactor/Cyclotron Production*	*Processing*	

** **Target** and transfer system from cyclotron to synthesis rig **may be considered as the first step of active substance manufacture**.*

4. The manufacturer of the final radiopharmaceutical should **describe and justify** the steps for manufacture of the active substance and the final medicinal product and which GMP (part I or II) applies for the specific process/manufacturing steps.

EudraLex Vol. 4 Part II: API manufacturing

Table 1: Application of this Guide to API Manufacturing

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging

- Production of **API Starting Material is not subject to GMP**
- Nuclear transformations are not listed => supports exclusion from GMP requirement
- Even less strict requrements in GMP for investigational Medicinal Products

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What are the experts' opinions (regulators) on the GMP requirement of a radionuclide used for preparation of an Investigational Medicinal Product intended to be applied in early phase clinical trials?

Answers

- Starting materials for IMPs (i.e. radionuclides) do not require GMP status. Also, more generally, radionuclides may not require GMP status if they are supplied as non-sterile starting material.

- ….non-GMP radionuclides have to be implemented into a GMP compliant process by the producer (and applicant) of the final IMP. For this a well-defined and controlled reproducible radionuclide production process is required and these data must be included …..

+ ……..

European Medicines Agency: GMP/GDP Inspectors Working Group Response to PRISMAP question - Eudralex Volume 4 GMP - Annex 3

- ….. **Updating Annex 3 with guidance to clarify applicability of GMP part I, II or GMP for IMPs and to remove the statement, 'this annex is also applicable to radiopharmaceuticals used in clinical trials'**.

Although there are some exclusions of some specific Investigational Medicinal Products (IMP's) from the requirements of Good Ma… rad…

Fur… the pro… rob… uire cor… adv…

It is…

- **Ex…**

- The GMDP IWG have however agreed that a review and update of Annex 3 is needed in light of scientific progress and this will be added to the next GMDP IWG work programme that will be published in early 2024. The IWG will seek and welcome views of stakeholders during this revision phase.

- Work programme states target date of Q4 2026!!

It is acknowledged that some isolating steps might not be traditional, however it is the opinion of the GMDP IWG that this should not be the basis to exclude these from adhering to (basic) GMP principles set out in EudraLex Volume 4, Part II Basic Requirements for Active Substances used as Starting Materials.

Not all chemical and physical processes to isolate radionuclides should be exempt from GMP and **the stringency** of the application of GMP to active substance manufacturing **should increase as the process proceeds from early steps to final steps**, purification, and packaging. The decision to exclude some isolation steps from GMP should be made on a **case-by-case basis** by the manufacturer considering the entire process and based on an appropriate risk assessment.

Revision of EU`s Pharmaceutical Legislation Commission proposal May 2023

- **In relation to radiopharmaceuticals**

……. Bloody little

Recital:

- …. In the case of radiopharmaceuticals used for therapy, marketing authorisations, posology and administration rules have to **notably respect** that Directive's requirements that **exposures of target volumes** are to be **individually planned**, and their **delivery appropriately verified ….**

→ **Not followed by any relevant text in the Articles**

- ASMF file certificate (may allow harmonized access by Agencies to evaluation of e.g. precurosors)

Articles:

- **Art. 16: No MA for generators, kits and radionuclide precursors when used as starting materials (within a MA of the end product)**

No change in definitions, inclusion of Radiopharmaceuticals into hosptial excemptions or in relation to GMP rules…

Proposal to change Definitions

- Include Radionuclides into the **definition of substances and starting materials**
- ***Radiopharmaceutical:*** Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose. → **Explain more clearly „medicinal purpose“ and describe exclusion criteria (radionuclides only, sealed sources), explain „radionuclide“- and „complex“ radiopharmaceuticals**
- ***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. → **explain that it can be used as radiopharmaceutical or as radionuclide for radiolabelling**
- ***Kit:*** Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration. → **Explain the „preformulated“ nature of kits, clear differentiation from casssettes and „reagent sets“**
- ***Radionuclide precursor:*** Any other radionuclide produced for the radiolabelling of another substance prior to administration.→ **Remove this definition, only in combination with a kit ASMF submission or separate MA**

→*Accepted in a first revision proposal by the Parliament, removed in the final version, no changes to be expected in the final version*

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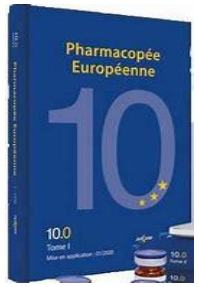
QUALITY OF THE RADIOLANTHANIDES

The European Pharmacopoeia Convention



Details of Treaty No.050

Title	**Convention on the Elaboration of a European Pharmacopoeia (ETS No. 050)**
Reference	**ETS No. 050**
Opening of the treaty	**Strasbourg 22/07/1964 - Treaty open for signature by the member States which take part in the activities in the field of public health referred to in Resolution (59)23 and for accession by other member States and by non-member States**
Entry in force	**08/05/1974 (8 Ratifications.)**
Summary	The Convention aims to harmonise specifications for medicinal substances in their original state or in the form of pharmaceutical preparations. The Parties undertake progressively to elaborate a European pharmacopoeia. The European Pharmacopoeia becomes the official standard applicable within the respective Parties. It is drawn up by the European Pharmacopoeia Commission which determines the general principles applicable to the elaboration of the European Pharmacopoeia, decides upon methods of analysis, arranges for the preparation of and adoption of monographs to be included in it, and recommends the fixing of the time limits within which its decisions of a technical character are to be implemented within the territories of the Parties. The European Pharmacopoeia Commission operates under the overall supervision of the Public Health Committee.

→ Legally binding in member states (e.g. defined in drug legislation)

Pharm Eur radionuclide precursor monographs

- *Generators: Monograph is for the eluate, not for the generator*

Sodium pertechnetate (^{99m}Tc) injection (fission)

01/2008:0124
corrected 7.0

SODIUM PERTECHNETATE (^{99m}Tc) INJECTION (FISSION)

Natrii pertechnetatis (^{99m}Tc) fissione formati solutio iniectabilis

This monograph applies to sodium pertechnetate (^{99m}Tc) injection obtained from molybdenum-99 extracted from fission products of uranium. Sodium pertechnetate (^{99m}Tc) injection obtained from molybdenum-99 produced by neutron irradiation of molybdenum is described in the monograph Sodium pertechnetate (^{99m}Tc) injection (non-fission) (0283).

DEFINITION

Sterile solution containing technetium-99m in the form of pertechnetate ion and made isotonic by the addition of sodium chloride. The injection may be prepared from a sterile preparation of molybdenum-99 under aseptic conditions.

Technetium-99m: 90 per cent to 110 per cent of the declared technetium-99m radioactivity at the date and time stated on the label.

GALLIUM (^{68}Ga) CHLORIDE SOLUTION FOR RADIOLABELLING

Gallii (^{68}Ga) chloridi solutio ad radio-signandum

$^{68}GaCl_3$ M_r 174.3

DEFINITION

Solution containing gallium-68 in the form of gallium chloride in dilute hydrochloric acid. The preparation may contain acetone.

Content:

– *gallium-68*: 90 per cent to 110 per cent of the declared gallium-68 radioactivity at the date and time stated on the label.

CHARACTERS

Appearance: clear, colourless solution.

Half-life and nature of radiation of gallium-68: see general chapter *5.7. Table of physical characteristics of radionuclides.*

Lutetium (^{177}Lu) solution for radiolabelling

07/2017:2798
corrected 9.3

LUTETIUM (^{177}Lu) SOLUTION FOR RADIOLABELLING

Lutetii (^{177}Lu) solutio ad radio-signandum

$^{177}Lu^{3+}$ M_r 176.9

DEFINITION

Solution containing lutetium-177 in the form of lutetium(III) ion in dilute hydrochloric acid.

Content:

– *lutetium-177*: 90 per cent to 110 per cent of the declared lutetium-177 radioactivity at the date and time stated on

European Pharmacopoeia Ed 11.3-11.6

Radiopharmaceuticals

New:

- Gallium (^{68}Ga) DOTANOC injection (3051)
- Gallium (^{68}Ga) oxodotreotide injection (3050)

To complete the series of ^{68}Ga labelled edotreotide like compounds (DOTATOC, DOTANOC AND DOTATATE) monographs. Only slight differences between the three monographs.

- *In Ed 11.6:*

- Ioflupane (^{123}I) injection (3144)

- *In Ed 11.7: (?)*
- Lutetium (^{177}Lu) zadavotide guraxetan injection: 1st therapeutic PSMA monograph, adopted in March 2024

Quality Control zadavotide guraxetan

Specifications and release Lu-177 PSMA I&T

Parameter	Method	Specification	Prior to release
pH	pH indicator strip	4 – 7	x
Identity HPLC	HPLC	t_R (Lu-177-PSMA I&T) matches standard	x
Radionuclidic identity	Gamma ray spectrometry	According to reference	
Chemical purity and content	HPLC	Lu-PSMAIT, PSMAIT and related impurities (Rt 5-12min) NMT <20µg /GBq	x
	GC	Ethanol NMT 10 % (v/v)	
Radiochemical purity TLC	HPLC	[^{177}Lu]Lu-PSMA I&T NLT 95 %	x
	TLC (0,1M Citrat pH5)	free[^{177}Lu]: NMT 2 %	x
MICROBIOLOGY			
Bacterial Endotoxins	LALPh. Eur. 2.6.14 Method C	NMT 8.75 EU / ml (eq to 185/V, 20ml max volume)	X
Sterility	Ph. Eur. 2.6.1	Sterile	

WP4 – Harmonisation & Standardisation

Tb-161 Quality - Monograph development

- Drafting a **Monograph** (SCK CEN, PSI, NCBJ) and started to develop standardised analytical methods to provide harmonised specifications across

N.C.A.·TERBIUM°(^{161}TB)·CHLORIDE·SOLUTION·FOR·RADIOLABELLING¶

N.c.a.·Terbium·(^{161}Tb)·chloridi·solutio·ad·radio-signandum¶

¶

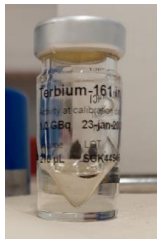
$^{161}Tb^{3+}$¶

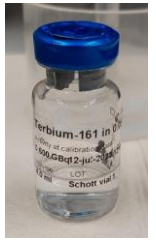
M_r°161¶

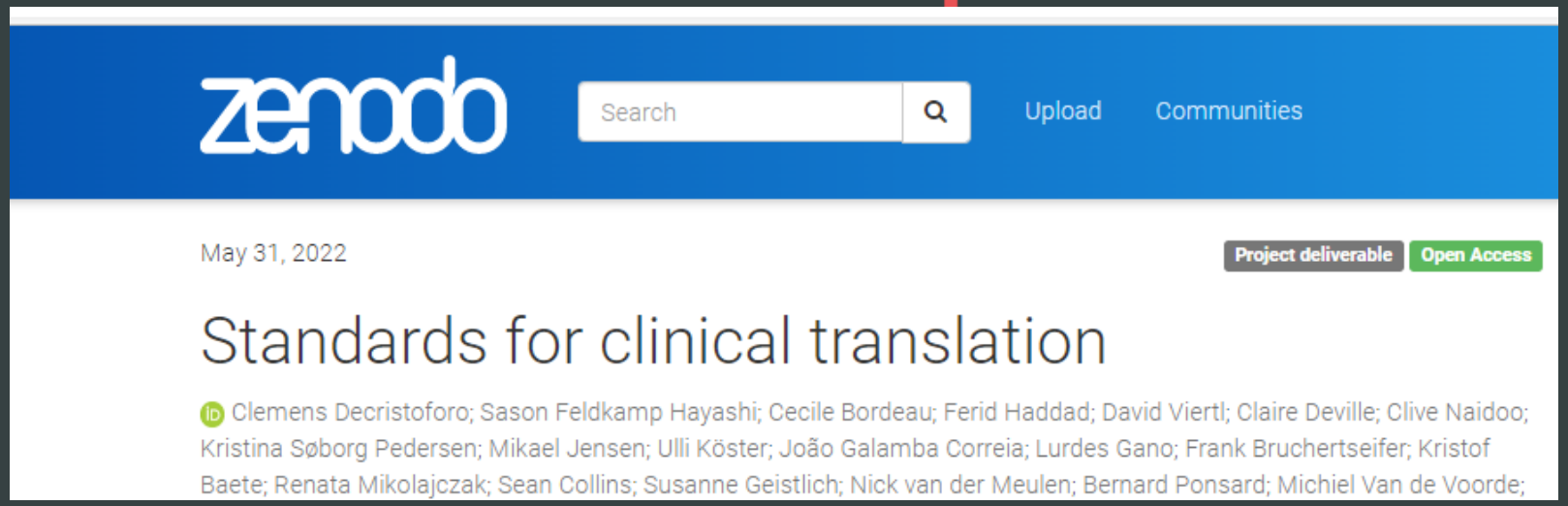
DEFINITION¶

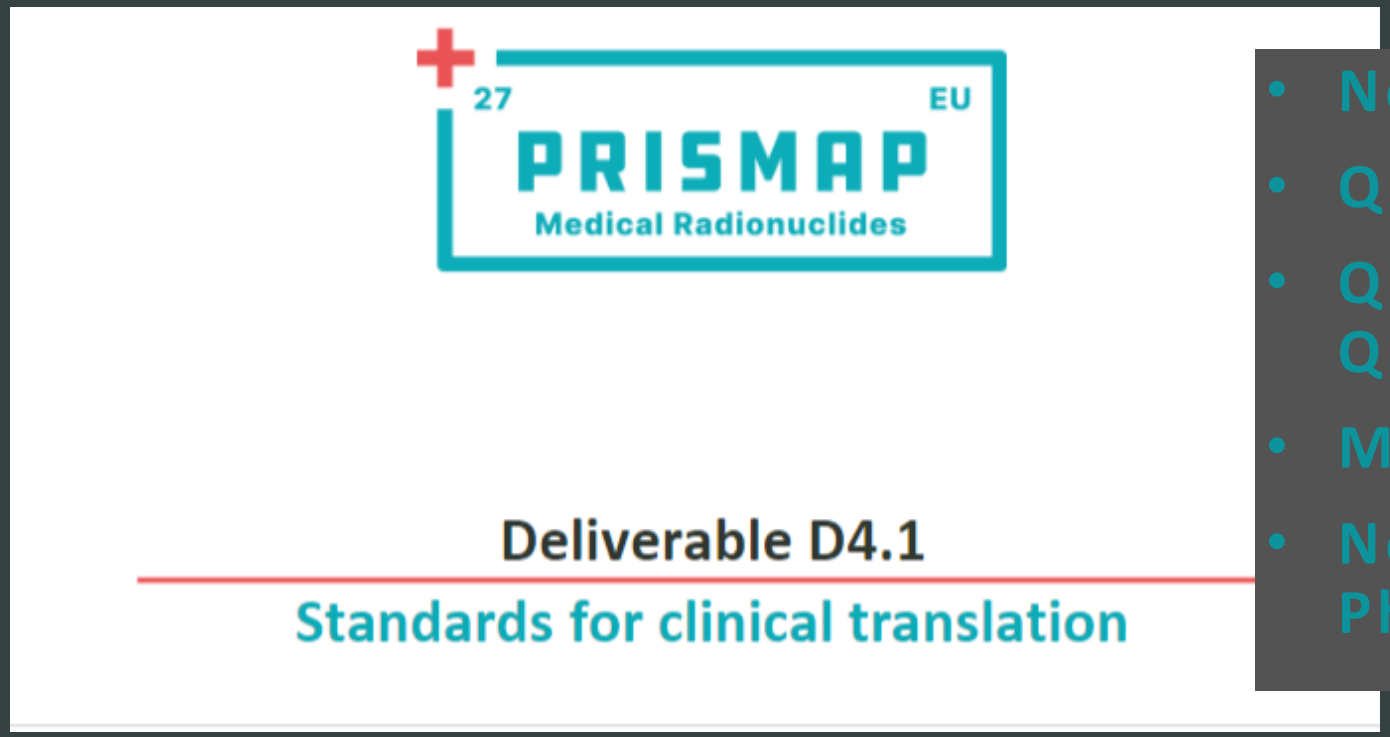
Solution·containing°Terbium-161·in·the·form·of°Terbium(III)·ion·in·dilute·hydrochloric·acid.¶

- **Tb-161 NMES study:** measurement of reference different calibration factors of Tb-161, geometry influence









- Nomenclature
- Quality: Production & GMP
- Quality: Specifications and Quality Control
- Metrology and Medical Physics
- Non Clinical Safety & Pharmacology

Rising awareness of requirements for Medical Radioisotopes in the EU

- Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) ..in support of Europe's Beating Cancer Plan
  - SIMPLERAD Project (Study on the Implementation of the Euratom and EU Legal Bases with Respect to the Therapeutic Uses of Radiopharmaceuticals)
  - European Radioisotope Valley Initiative (ERVI)

- Research projects funded ("focus "Theranostics")
  - PRISMAP grant agreement No 10100857
  - SECURE

- European Pharmacopoeia: Quality Standards for Medical Radionuclides

- European Association of Nuclear Medicine EANM

European Commission

Simplerad

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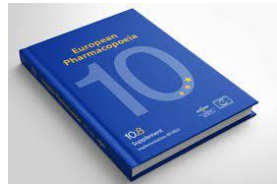
SECURE

edqm European Directorate for the Quality of Medicines & HealthCare



EANM EUROPEAN ASSOCIATION OF NUCLEAR MEDICINE

27 EU P Prismap

THANK YOU FOR YOUR ATTENTION

The PRISMAP Radiolanthanides Workshop

Feel free to contact:
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(I will answer unless I am skiing or travelling)