A BUMPY ROAD TO STANDARDISE AND HARMONISE THE REGULATORY REQUIREMENTS FOR RADIOPHARMACEUTICAL PRODUCTION INVOLVING NOVEL RADIONUCLIDES

WP4 activities

CM9 Warsaw, November 19th 2025

Clemens Decristoforo

Department of Nuclear Medicine

Medical University of Innsbruck, Innsbruck, Austria

Radioactive substances used 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 Radionuclides used in a sealed source for treatment (e.g. microspheres)

→ **Medical device**

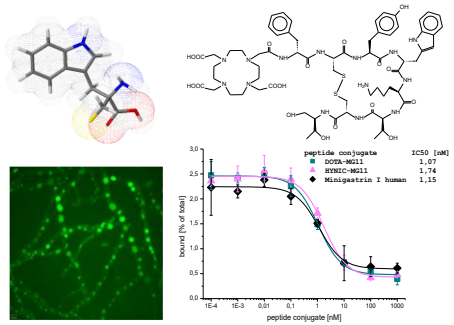
Path of a „new“ Radiopharmaceutical to the patient

MEDIZINISCHE UNIVERSITÄT INNSBRUCK
UNIVERSITÄTSKLINIKEN

Data generation

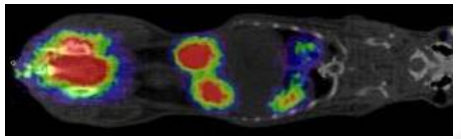
Radionuclide Production → **Quality**

„Cold“ chemistry → Radiochemistry → **Quality**

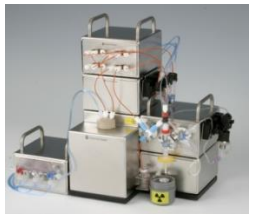


Biological characterization in vitro → **Safety and Efficacy**

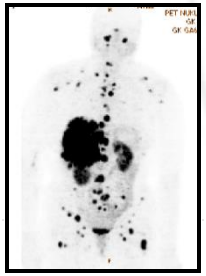
Biological characterization in vivo



Pharmaceutical formulation → **Quality**
Safety and efficacy



Clinical Trial → **Safety and Efficacy**



Medicinal Product

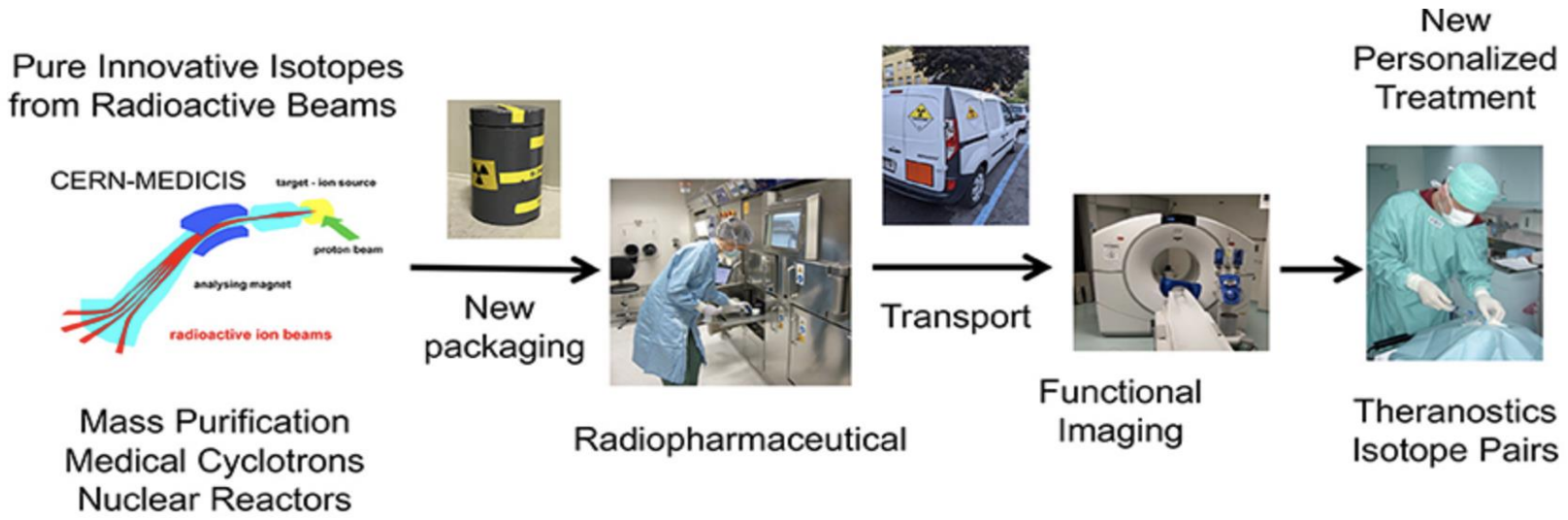
PRISMAP WP4: Regulatory Topics: Novel Medical Radionuclides for Radiopharmaceuticals

Define and harmonise common standards in the production of non-conventional radionuclides and translational research in view of regulatory requirements for clinical applications

Support consortium in **clinical translation** of novel radiopharmaceuticals

Provide **standardised quality and safety data and documentation** for radionuclides and radiopharmaceuticals both for the consortium and the clinical research community

MEDIZINISCHE UNIVERSITÄT INNSBRUCK



The trip of PRISMAP`s Workpackage 4 to Standardisation and Harmonisation from 2021-2025

Not always straight and smooth

27 EU P Prismap

SPEAKERS

Overseas Experts

Serge Lyashchenko	MSKCC/US
Cathy Cutler	BNL/US
Jeff Norenberg	UNM/ USA
Kohshin WASHIYAMA	FMU/J

Industry Experts

Konstantin Zhernosekov	ITM/D
Cristiana Gameiro	IBA/B

International Organisations

Aruna Korde	IAEA/A
Oliver Kiss	EANM/D
Michael Lassmann	EANM/D

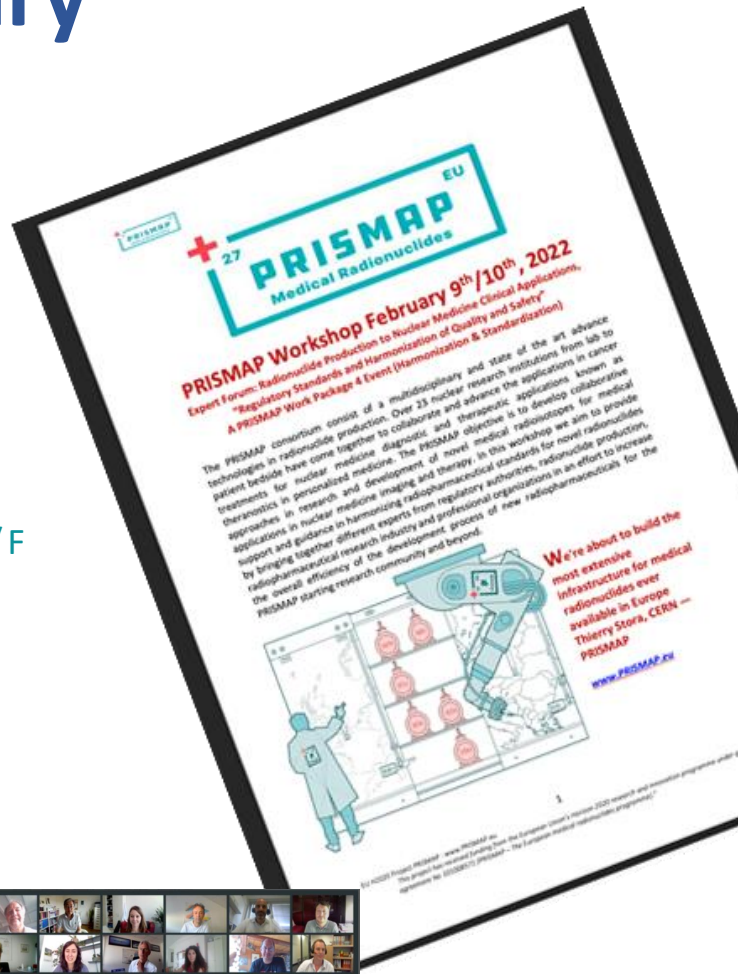
Regulatory Experts

Günter Waxenecker	AGES / A
Francesco Pignatti	EMA/NL
Thijs Kroon	NL
Fernando Blanco	AEMPS/E
Jose R. Cozar Ruiz	EMA/NL
Rolf Hesselmann	BAG/CH

First Stop: Workshop February 2022

PRISMAP`s Experts

Renata Mikolajczak	NCBJ/PL
David Viertl	CHUV/CH
Clemens Decristoforo	MUI/A
Sean Collins	NPL/UK
Kristof Baete	KUL/B
Ferid Haddad	ARRONAX/F
Frank Bruchertseifer	JRC/D
Thierry Stora	CERN/CH
Ulli Koester	ILL/F
Mikael Jensen	DTU/DK



+ WP4 members

+ Participants

zenodo Search Upload Communities

May 31, 2022

Project deliverable Open Access

Standards for clinical translation

Clemens Decristoforo; Sason Feldkamp Hayashi; Cecile Bordeau; Ferid Haddad; David Viertl; Claire Deville; Clive Naidoo; Kristina Søborg Pedersen; Mikael Jensen; Ulli Köster; João Galamba Correia; Lurdes Gano; Frank Bruchertseifer; Kristof Baete; Renata Mikolajczak; Sean Collins; Susanne Geistlich; Nick van der Meulen; Bernard Ponsard; Michiel Van de Voorde;

Workshop February 2022

27 EU PRISMAP Medical Radionuclides

Deliverable D4.1

Standards for clinical translation

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

→ Clarification of regulatory approaches needed

European Commission Revision of Pharmaceutical Directive 2001/83 Explanatory Memorandum and the Annexes 1 through 8 (April 2023): *PRISMAP Proposal*

PRISMAP welcomes the European Commission´s proposal for a revision, as well as, the efforts and commitment of the European Parliament to ensure that the regulatory framework for medicinal products, including radiopharmaceuticals based on nove radionuclides, is not only adapted to support the current practice, but also fosters innovation and secures patient access for the future.

To support this aim, PRISMAP proposes to **adapt EC`s proposal for a new directive 2023/0132 (COD)** and to ameliorate with the following aspects:

1. **Definitions (article 4) should reflect today's nuclear medicine and radiopharmacy practices. Updated definitions** (substance, radiopharmaceuticals, kit, generator…) will lay the **foundation** of an **updated regulatory framework** with adjustments for **unique aspects of novel Radionuclides.**
2. **Clarification of marketing authorization requirements** for the use of novel radionuclides
3. **Clarification** of the relation of **BSSD and Pharma Directive** (It is acknowledged that in Recital 19 of the proposed legislation reference is made to the Basic Safety Standards Directive (Council Directive 2013/59/Euratom), this should be further clarified and taken into consideration in the legal text itself).

European Commission Revision of Pharmaceutical Directive
PRISMAP Proposal

Comments on EU-Commission proposal for revision of pharmaceutical legislation released in April 2023

Proposal to revise definitions and regulatory texts on „radionuclide precursors“
Emails sent to MP`s, alignment with EANM Nov 2023

European Commission legislative proposal		European Parliament draft negotiating position		PRISMAP suggested amendment	Rationale/Justification
Recital 19	This Directive should be without prejudice to the provisions of Council Directive 2013/59/Euratom, ~~including with respect to justification and optimisation of protection of patients and other individuals subject to medical exposure to ionising radiation. 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 taking into account that doses to non-target volumes and tissues are to be as low as reasonably achievable and consistent with the intended therapeutic purpose of the exposure.~~	Amendment 5 – Recital 19	This Directive should be without prejudice to the provisions of Council Directive 2013/59/Euratom.	**Any rules governing radiopharmaceuticals must take into account the provisions of COUNCIL DIRECTIVE 2013/59/EURATOM of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation (2) and subsequent directives, the objective of which is to prevent the exposure of the general public, workers, volunteers or patients to excessive or unnecessarily high levels of ionising radiation, and in particular of Article 28 (a) and (c) thereof, which subjects the use of radioactive source to regulatory control of such medicinal products and Article 56 requiring for all medical exposure of patients for radiotherapeutic purposes, that exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.**	The introduction of Directive 2013/59/Euratom (BSS directive) requires to update the reference regarding specific authorization of the use of radioactivity in the context of medical applications (and with it radiopharmaceuticals), as rightly indicated by Article 4.1 of the Directive 2001/83/EC, i.e., community rules on medicinal products should not contradict the BSS Directive. Additionally the BSS directive has introduced the requirement to individually plan treatment involving ionising radiation, which includes therapy with radiopharmaceuticals. The missing alignment of the current directive 2001/83/EC with this requirement in the BSS directive has caused an unclear situation in Member States and should be clarified. It is acknowledged that in Recital 19 of the proposed legislation reference is made to the Basic Safety Standards Directive (Council Directive 2013/59/Euratom) which needs to be taken into consideration for Radiopharmaceuticals. However, neither the positioning (as a Recital) nor the verbatim quote of the Euratom Directive (which in the spirit of the European Commission's own pledge for regulatory harmonisation through SAMIRA Action Plan should be avoided) are expected to help in establishing a clear and feasible approach for radiopharmaceuticals which takes into account the major innovations in the field and aligns the regulatory provisions of BSSD and pharma legislation.
	(4) In cases where, taking into account all its characteristics, a product falls within the	Ø	Ø	4. In cases where, taking into account all its characteristics, a product falls within the definition of a 'medicinal	See the rationale for Recital 19.

- Most proposals were not considered
- Limited excemtions for radionuclides as starting materials
- Revision in the hands of Council (i.e. memberstates)
- Proposal to allow individual memberstates to excempt radionuclides from Marketing Authorisation requirement

IAEA
International Atomic Energy Agency

IAEA
TM Meeting on
Radiopharmaceutical Regulations
March 2023
Position paper in EJNMMI RPC in Jan. 2024

POSITION PAPER Open Access

Position paper to facilitate patient access to radiopharmaceuticals: considerations for a suitable pharmaceutical regulatory framework

Aruna Korde[1], Marianne Patt[2], Svetlana V. Selivanova[3,4], Andrew M. Scott[5,6], Rolf Hesselmann[7], Oliver Kiss[8], Natesan Ramamoorthy[9], Sergio Todde[10], Sietske M. Rubow[11], Luther Gwaza[12], Serge Lyashchenko[13], Jan Andersson[14,15], Brian Hockley[16], Ravindra Kaslival[17] and Clemens Decristoforo[18]*

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Abstract

Background: Nuclear medicine has made enormous progress in the past decades. However, there are still significant inequalities in patient access among different countries, which could be mitigated by improving access to and availability of radiopharmaceuticals.

Main body: This paper summarises major considerations for a suitable pharmaceutical regulatory framework to facilitate patient access to radiopharmaceuticals. These include the distinct characteristics of radiopharmaceuticals which require dedicated regulations, considering the impact of the variable complexity of radiopharmaceutical preparation, personnel requirements, manufacturing practices and quality assurance, regulatory authority interfaces, communication and training, as well as marketing authorisation procedures to ensure availability of radiopharmaceuticals. Finally, domestic and regional supply to ensure patient access via alternative regulatory pathways, including in-house production of radiopharmaceuticals, is described, and an outlook on regulatory challenges faced by new developments, such as the use of alpha emitters, is provided.

Conclusions: All these considerations are an outcome of a dedicated Technical Meeting organised by the IAEA in 2023 and represent the views and opinions of experts in the field, not those of any regulatory authorities.

Keywords: Radiopharmaceutical, Regulations, Legislation, Regulatory framework, GMP, Marketing authorisation

Communications with the EMA

- 2021: Meeting with EMA representatives
- 2022: EMA participation in Workshop
- 2023: Comments on EMA guidelines
- 2023: **EMA ITF briefing meeting**
- 2023: Comments on Annex 3 revision IWG
- 2024/2025: Comments on Concept paper on clinical evaluation of therapeutic radiopharmaceuticals in oncology

Reply to EMA`s Concept papers to revise guidelines

EMA – raising awareness and clarifying quality requirements for novel radionuclides

EMA Innovation Task Force Briefing meeting

4 questions regarding novel radionuclides in clinical trials

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/237805/2023
European Medicines Agency

ITF Briefing meeting report
PRISMAP The European Medical Radioisotope Program

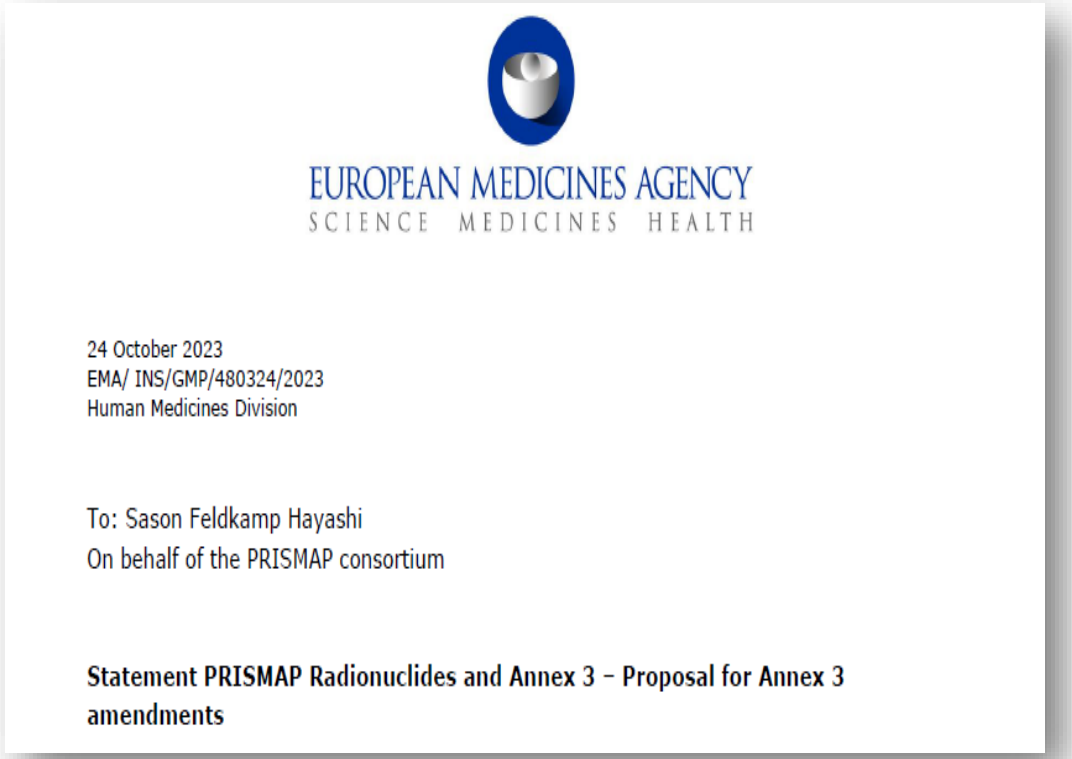
Briefing meeting held online with the European Medicines Agency (EMA) on 31/03/2023.

The objective of the ITF briefing meetings is to provide for a preparatory discussion on scientific and regulatory topics relevant to the development of new medicinal products and technologies complementing and reinforcing existing formal procedures.

Name/identifier:	Non-conventional Radionuclides
Applicant:	PRISMAP The European Medical Radioisotope Program
Product / technology / method / methodology description:	Radionuclide Production
Intended use:	Preparation of Radiopharmaceuticals for diagnosis and/or therapy

Inspectors Working Group, EMA

Reply to PRISMAP`s questions



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2023
EMA/ INS/GMP/480324/2023
Human Medicines Division

To: Sason Feldkamp Hayashi
On behalf of the PRISMAP consortium

Statement PRISMAP Radionuclides and Annex 3 – Proposal for Annex 3 amendments

EMA Innovation Task Force Meeting: Key Takeaway

- **No marketing authorization (MA) requirements** for novel PRISMAP radionuclides in Clinical trials
  - **The radionuclide that is used to prepare an Investigational Medicinal Product (IMP) does not need to hold a Marketing Authorisation (MA). Regulators need to know the manufacturing process of the radionuclide. The information required will be for example: which target and the composition, the target preparation, irradiation parameters and the purification separation process. This information is needed to evaluate the suitability of the radionuclide for the preparation of the radiopharmaceutical. The quality of the radionuclide solution for radiolabelling is closely bound to the manufacturing process.*

  Note: One may be GMP compliant but not have a Marketing Authorization.

- **No GMP requirements** for novel PRISMAP radionuclides in Clinical trials
  - **Therefore, non-GMP produced (novel) radionuclides may be supplied (by PRISMAP) for IMP production in clinical trials. GMP is required for the production process and therefore non-GMP radionuclides have to be implemented into a GMP compliant process by the radiopharmaceutical producer (and applicant) of the final IMP. For this a well-defined and controlled reproducible radionuclide production process is required for radiopharmaceutical production and these data must be included in the manufacturing description of the IMPD.*

- **EMA GMP/GDP Inspector Working Group**: Invitation to review Eudralex Volume 4 Annex 3

- **Radionuclidic and Radiochemical Purity requirements** cannot be defined in a general way, but remain a case-by-case evaluation based on the individual risk evolving from the related impurities.

- **EMA Network unanimously support**: Metrology for Clinical Implementation for a reliable and accurate determination of the amo of (radio)activity in a radiopharmaceutical.

27 EU P Prismap

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 EU PRISMAP Medical Radionuclides

Question to EMA (Innovation Task Force Meeting)

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:

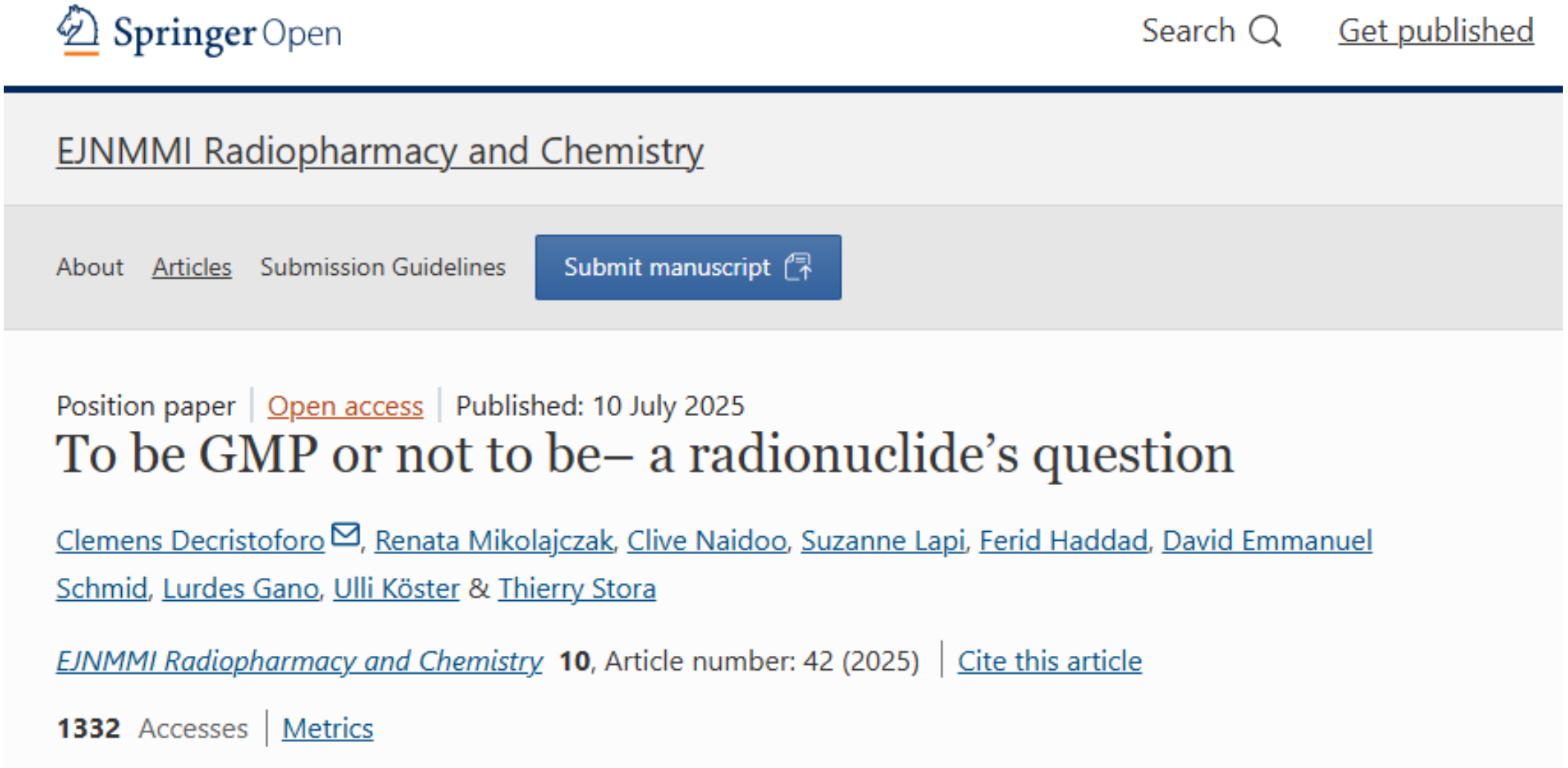
- *Starting materials for IMPs (i.e. radionuclides) do not require GMP status. Also, more generally, radionuclides may not require GMP status if they are supplied as non-sterile starting material.*
- *….non-GMP radionuclides have to be implemented into a GMP compliant process by the producer (and applicant) of the final IMP. For this a well-defined and controlled reproducible radionuclide production process is required and these data must be included ….. + ……..*

PRISMAP Proposals to IWG regarding GMP and Annex 3:

- **Clarification of the term radioactive precursor vs. radionuclide precursor**
- **Guidance to clarify the applicability of GMP part I, II or GMP for IMPs**
- **Update of the table that differentiates non-GMP and GMP based on scientific developments esp. in radionuclide production**

The GMDP IWG agreed that a review and update of Annex 3 is needed in light of scientific progress. Work programme states target date of Q4 2026!!

GMP or no GMP for radionuclides in clinical research



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Position paper | Open access | Published: 10 July 2025

To be GMP or not to be– a radionuclide's question

Clemens Decristoforo, Renata Mikolajczak, Clive Naidoo, Suzanne Lapi, Ferid Haddad, David Emmanuel Schmid, Lurdes Gano, Ulli Köster & Thierry Stora

EJNMMI Radiopharmacy and Chemistry **10**, Article number: 42 (2025) | Cite this article

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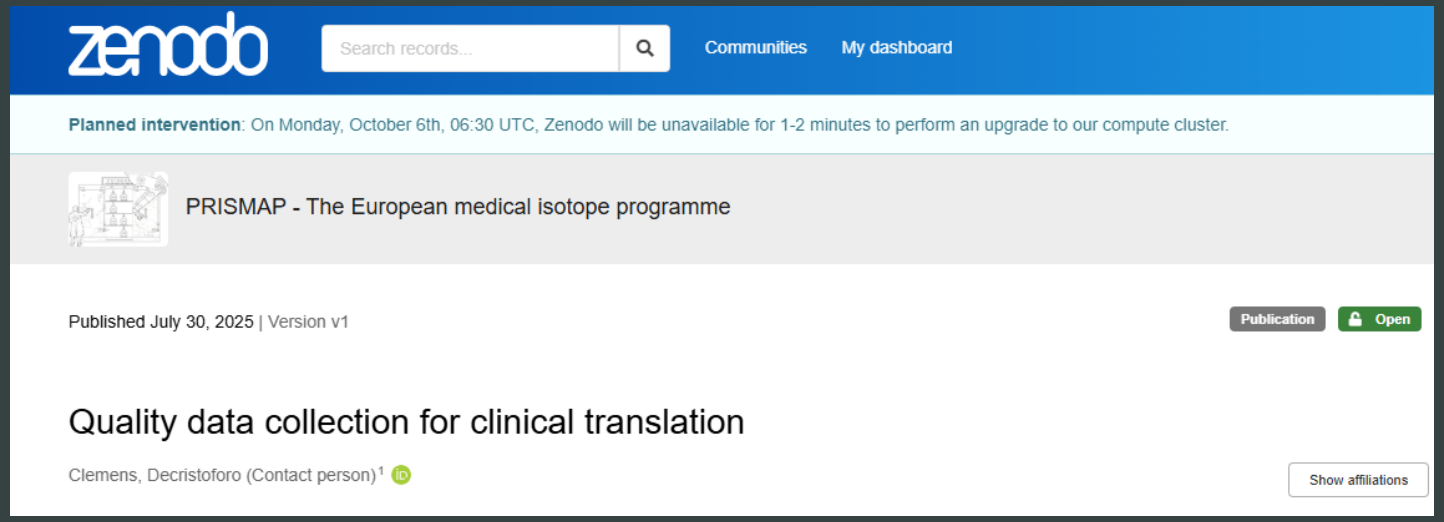
QUALITY ASPECTS OF SPECIFIC RADIONUCLIDES

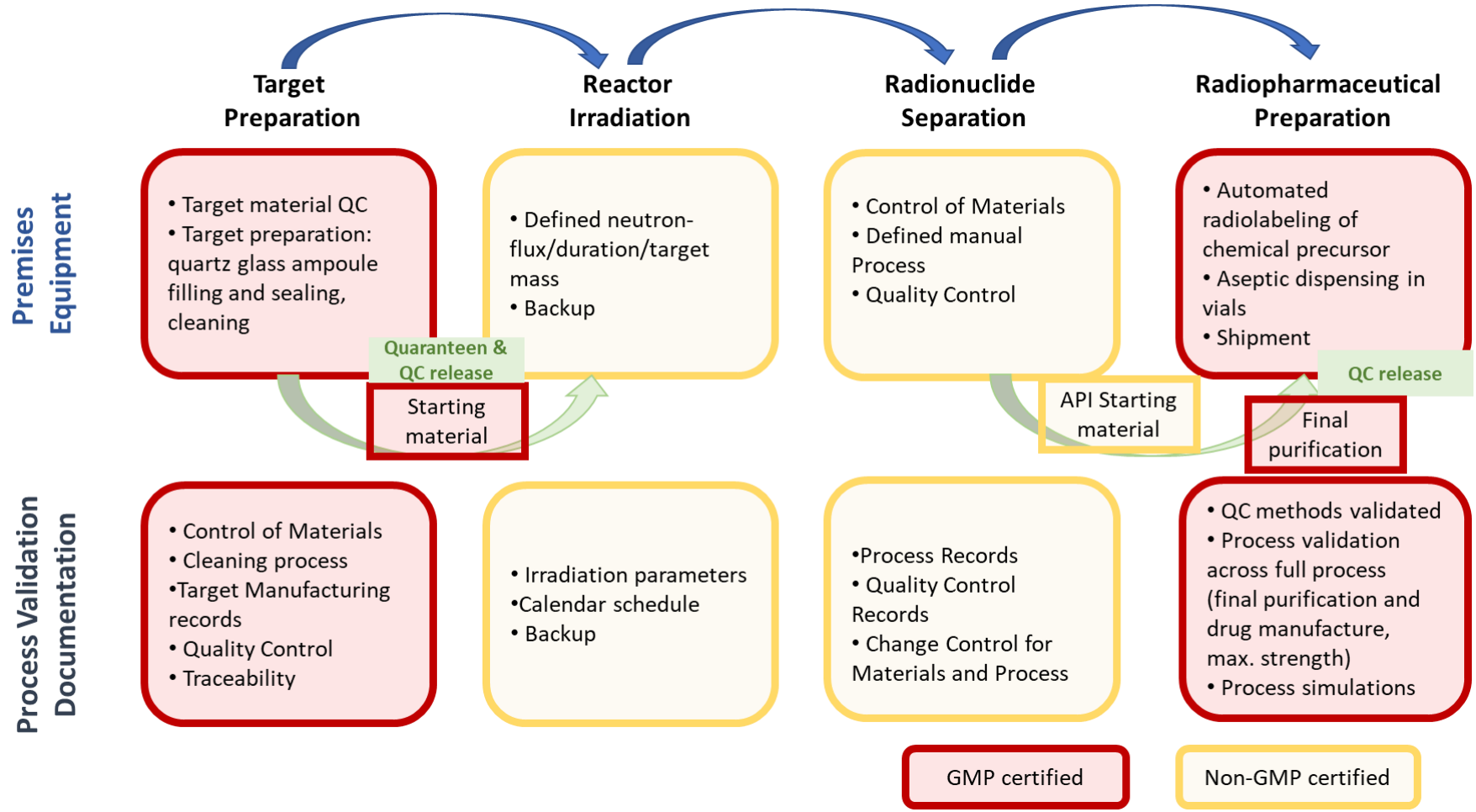


Tb 161

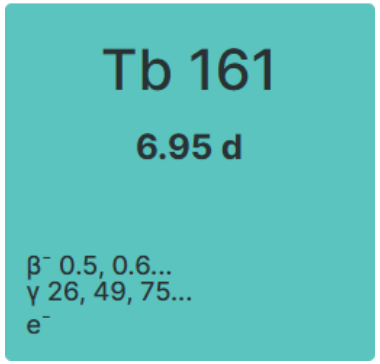
6.95 d

β^- 0.5, 0.6...
γ 26, 49, 75...
e^-

Manufacturing strategy for clinical ^{161}Tb-radiopharmaceuticals developed and approved by the Swiss national health-authority for first clinical trials in-human



Quality Control results of Tb-161 radiolabelling solution produced for PRISMAP users



		Date of Chemical Separation		
Parameter	Requirement	10.11.2023	09.04.2024	28.05.2024
RCP (HPLC)*	≥99%	99%	100%	100%
Identity (γ-spectrometry)	74.6 ± 1 keV 87.9 ± 1 keV 103.1 ± 1 keV 106.1 ± 1 keV	Complies	Complies	Complies
RNP at Expiry Date (γ-spectrometry)	Tb-160 ≤ 0.1% Tb-161 ≥ 99.9%	< 0.1% > 99.9%	< 0.1% > 99.9%	< 0.1% > 99.9%

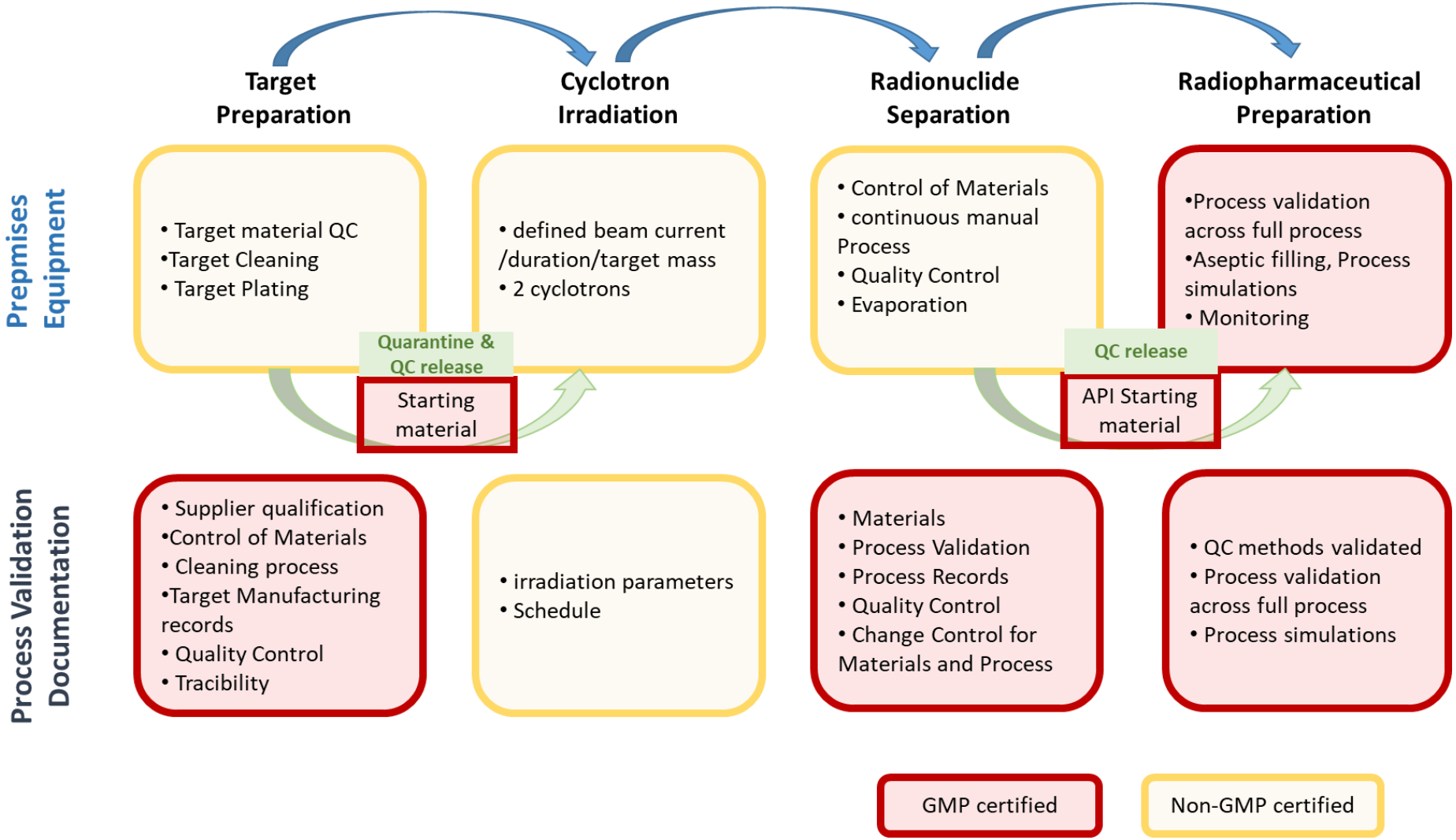
Metals in Tb-161 solutions determined by ICP OES

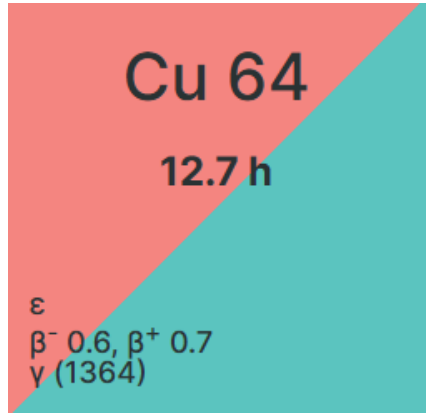
	NCBJ				
Elements	01/24	02/24	03/24	04/24	01/25
			[ppm]		
Cu	0.111	< 0.892	1.92	< 0.586	< 3.58
Co	0.185	< 0.529	< 1.68	< 0.647	< 0.376
Fe	0.167	< 0.068	< 0.117	< 0.405	< 0.372
Ni	< 0.116	< 0.839	< 2.00	< 0.376	< 0.720
Pb	< 0.439	< 0.574	< 2.71	< 1.90	< 1.13
Zn	0.431	0.823	4.25	1.58	1.52
Gd	5.41	6.41	12.5	4.25	< 3.10
Tb	3.76	< 2.10	1.99	< 1.77	< 4.51
Dy	0.224	< 0.343	0.637	0.425	< 3.12

Quality requirements

Identity tests
Radionuclidic purity
Radiochemical purity
Metal determination
Apparent molar activity (AMA) determination
pH
Sterility and endotoxins
Labelling

Manufacturing strategy for ^{64}Cu-radiopharmaceuticals used for compassionate use and clinical trials developed and approved by the Danish Health Authority





WP4 – Harmonisation & Standardisation

- **Task 4.2** on **Quality** of novel radionuclides and radiopharmaceuticals:
- **Cu-64**: Inter-laboratory Comparison (**ILC**) study with **Cu-64**

Interlaboratory Comparison Study

Arronax receiving and testing samples from 4 different producers centrally:

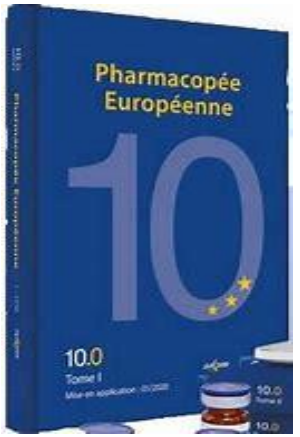
Activity
Volume
Metals and S.A. by ICP-MS
AMA Test

Institute	Production	Date	AMA [MBq/nmol] DOTA titration	MA [MBq/nmol] ICP	ESA [MBq/nmol] ICP
DTU	64Ni(p,n)64Cu	14/02/2022	1060	3225*	118**
PSI	64Ni(p,n)64Cu	10/10/2023	53	197	45
ARRONAX	64Ni(d,2n)64Cu	07/02/2024	78	72 (69)	48
NCBJ	63Cu(n,γ)64Cu	31/01/2024	0.012	Nd***	0.014

* determined from DTU ICP data, Calculated from Cu 0.31nmol/GBq
** determined from DTU ICP data, Calculated from Ni+Zn+Fe+Cu 8.47nmol/GBq
*** assumed that only Cu-is present
n.d.: not determined

More regulatory developments
EDQM and Pharm Eur Monograph

- **Apparent Molar Radioactivity (AMR) of radiometal solutions for radiolabeling**
  - Limit Test Method in development
- **Copper (^{64}Cu) solution for radiolabelling**
  - Monograph, in development
- **Actinium (^{225}Ac) for radiolabelling**
  - Chapter in development



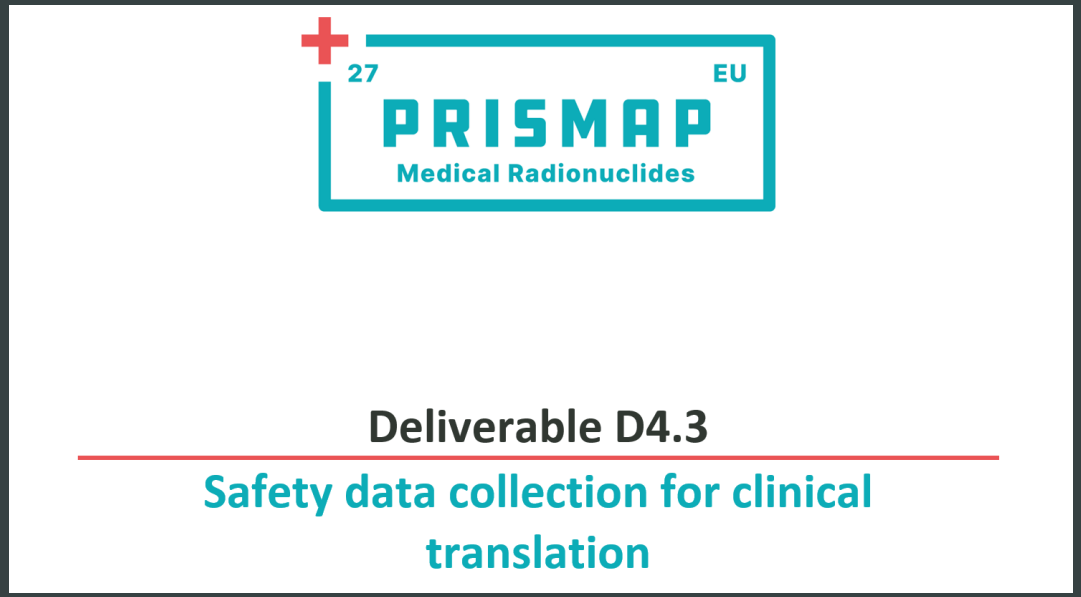
27 EU PRISMAP Medical Radionuclides

PRISMAP`s data an important contribution

Deliverable D4.2

Quality data collection for clinical translation

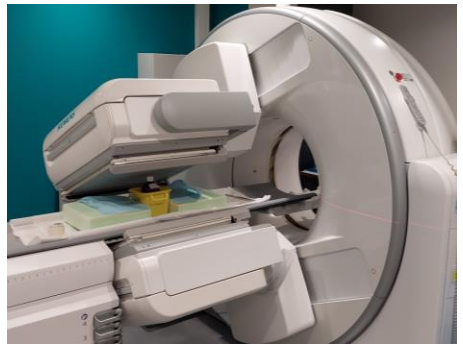
SAFETY DATA FOR NOVEL RADIONUCLIDES



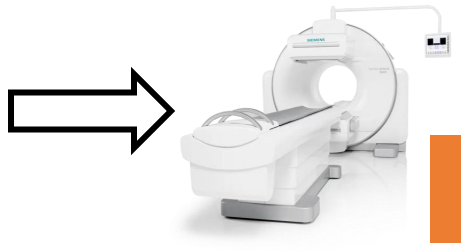
KU LEUVEN

Nuclear medicine equipment standardization (NMES)

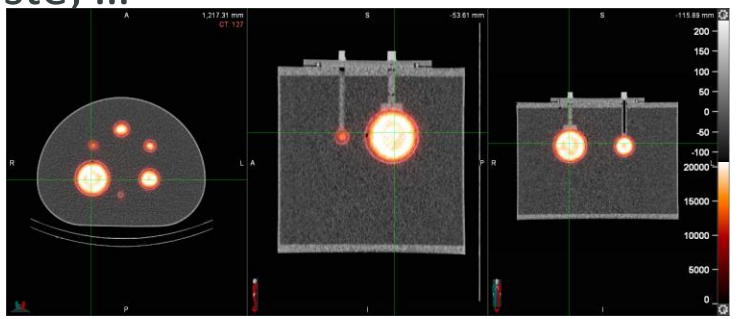
- Nuclear metrology: indispensable for the supply of novel radionuclides (SCK, NPL)
  - nuclear data – standardized recipients – traceable activities – CoA with *accuracy* information
- Medical physics: bridge gaps between radiopharmacy and (pre)clinics
  - activity meter calibration & verification – influence of recipient geometry
  - primary & secondary calibration factors – quality assurance & control
  - calibration of emission tomography equipment (SPECT, PET) – precision
  - involvement of a gamma counter for assistance during calibration efforts
- NMES using **Tb-161** provided by SCK (2023-25) & using Lu-177
  - calibration of multiple activity meters, gamma counter & SPECT/CT
  - addressed many practical challenges with suppliers and device manufacturers
  - non-clinical use, logistics, chemistry, waste, …



traceable activity



reliable quantification

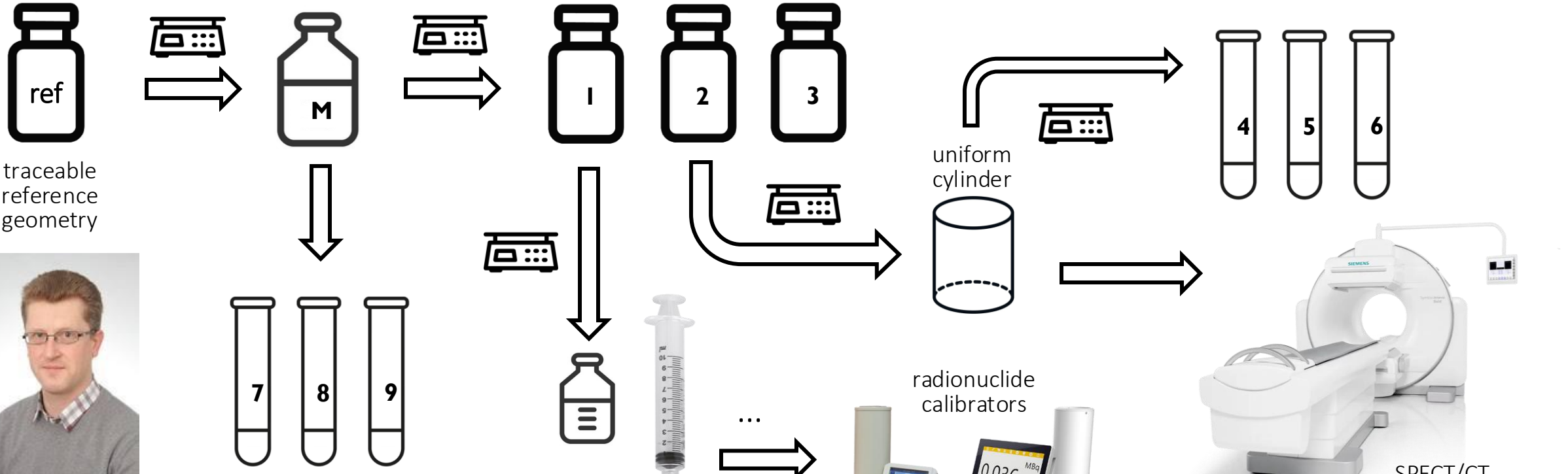


Calibration layout example

Nuclear medicine equipment standardisation for clinical translation: a case study with Tb-161 EANM presentation

mass derived

samples for gamma counter verification



master solution

derived reference geometries

traceable reference geometry

uniform cylinder

radionuclide calibrators

SPECT/CT

variety of recipients

KU LEUVEN

27 EU P Prismap

Collecting Safety Data reported from clinical application of Ac-225

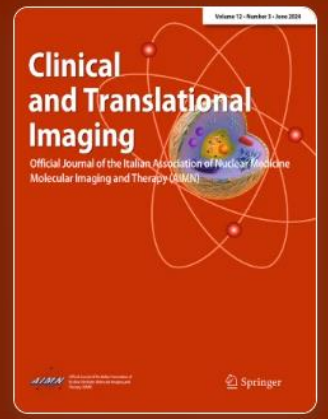
Hematologic (218)
Xerostomia (39)
Renal (34)
Hepatic (9)

PSMA ligands

Navigating the safety profile of Actinium-225 targeted alpha therapy: a comprehensive review

Review | Open access | Published: 04 November 2025

(2025) Cite this article



Clinical and Translational Imaging

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(n=229)

PRISMAP embedded in a European landscape with rising awareness of requirements for Medical Radioisotopes

- 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")
  - SECURE, ACCELERATE.EU, ALPHAMET
  - And….
- European Pharmacopoeia: Quality Standards for Medical Radionuclides
  - Monograph on Cu-64, Chapter on Ac-225
- European Association of Nuclear Medicine EANM, PRAC

European Commission

Samira Action Plan

Simplerad

27 EU PRISMAP Medical Radionuclides

SECURE

edqm European Directorate for the Quality of Medicines & HealthCare

EANM EUROPEAN ASSOCIATION OF NUCLEAR MEDICINE

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PRISMAP promoting standardisation and harmonisation activities

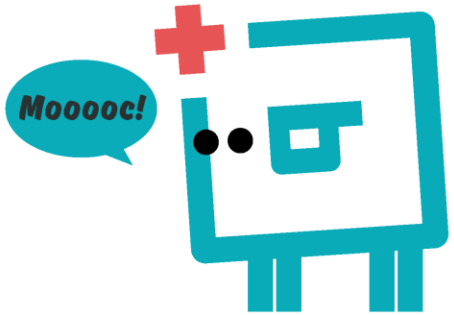
Workshops and Summerschools

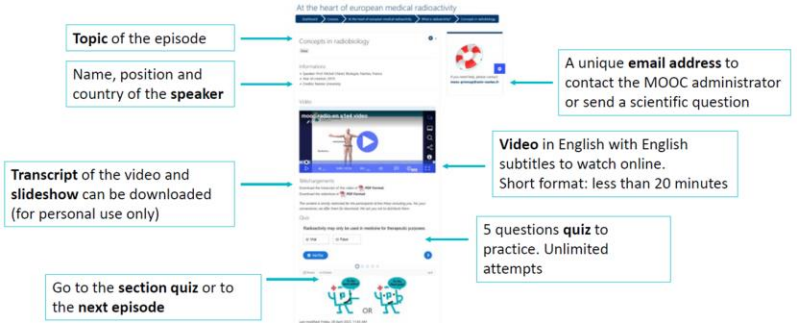
@EANM

@EU

@IAEA

JRC
EUROPEAN COMMISSION





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The trip of PRISMAP`s hopefully continues

House of Harmonisation

House of Standardisation

Re-Fuelling for PRISMAP+

27 EU

PRISMAP

Medical Radionuclides

THANK YOU FOR YOUR ATTENTION

AND THANKS TO ALL THE WP4 MEMBERS