Deliverable D4.1

Standards for clinical translation

Project Acronym	**PRISMAP**
Project Title	**The European medical isotope programme: Production of high purity isotopes by mass separation**
Grant Agreement No.	**101008571**
Topic	**INFRAIA-02-2020: Integrating Activities for Starting Communities**
Project start date	**01 May 2021**
Nature	**Report**
Dissemination level	**Public**
Due date	**M12**
Date of delivery	**M13**
Lead partner	**MUI**
Contributing partners	**ARRONAX, CHUV, DTU, CERN, ILL, IST-ID, JRC, KULeuven, NCBJ, PSI, SCK CEN, TUM**
Authors	**Cécile Bourdeau, Ferid Haddad (ARRONAX); David Viertl (CHUV); Claire Deville, Clive Naidoo, Kristina Søborg Pedersen, Mikael Jensen (DTU); Ulli Köster (ILL); João Galamba Correia, Lurdes Gano (IST-ID); Frank Bruchertseifer (JRC); Kristof Baete (KULeuven); Clemens Decristoforo, Sason Feldkamp Hayashi (MUI); Renata Mikolajczak (NCBJ); Sean Collins (NPL); Susanne Geistlich, Nick van der Meulen (PSI); Bernard Ponsard, Michiel Van de Voorde (SCK CEN); Monica Campillos (TUM)**
Reviewers	**Cathy S. Cutler (BNL, USA), Guy Bormans (KULeuven), Roger Schibli (PSI)**

Point of Contact	**Clemens Decristoforo and Sason Feldkamp Hayashi**
Institution	**MUI**
E-mail	**Clemens.decristoforo@i-med.ac.at, Sason.hayashi@i-med.ac.at**
Phone	**+43 51250480951, +43 51250422651**

Revision History

Version	Date	Author	Comment
0.1	07.04.2022	WP4 members	First draft
0.2	20.04.2022	WP4 members	Implemented reviews Cathy Cutler, Roger Schibli and WP4 meeting Apr.20th 16:30
0.3	21.04.2022	WP4 members	Implemented reviews Guy Bormans
0.45	21.04.2022	Kirsten Leufgen, Iris Dimbwadyo	Revision and completion, formatting
	26.04.2022	General Assembly	Review and approval
	09.05.2022	Thierry Stora	Review by the coordinator
0.95	10.05.2022	Iris Dimbwadyo	Implementation of suggestions proposed by the coordinator and the lead partner
1.0	13.05.2022	Kirsten Leufgen	Final version, approved by coordinator and general assembly

Contents

Abbreviations, Participant short names

Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
AMA	Apparent Molar Activity
API	Active Pharmaceutical Ingredient
ART	Activity Reference Time
BIPM	Bureau International des Poids et Mesures
Bq	Becquerel
c.a.	Carrier-added
CA	Consortium Agreement
CCRI	Consultative Committee for Ionising Radiation
CE	European Conformity
CoA	Certificate of Analysis
CTD	Common Technical Document
CZT	Cadmium-zinc-telluride
DG	Drafting Group
DICOM	Digital Imaging and Communications in Medicine
DNA	Deoxyribonucleic acid
DoA	Description of Action
EANM	European Association of Nuclear Medicine
EARL	EANM Research GmbH
EDQM	European Directorate for the Quality of Medicines & HealthCare
EDQM	European Directorate for Quality of Medicines and Healthcare
EFOMP	European Federation of Organisations for Medical Physics
EMA	European Medicines Agency
EURAMET	European Association of National Metrology Institutes
FDA	U.S. Food and Drug Administration
Fe	Iron
FIH	First in Human
GA	Grant Agreement
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPU	Fast Graphics Processing Unit

Gy	Gray
HCL	Hydrochloric Acid
HPLC	High Performance Liquid Chromatography
IAEA	International Atomic Energy Agency
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
IEC	International Electrotechnical Commission
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
ISO	International Organization for Standardization
LET	Linear Energy Transfer
MA	Marketing Authorization
MDR	Medical Device Regulation
MetroMRT	Metrology for Molecular Radiation Therapy
MIRD	Medical Internal Radiation Dose
MOBY	Realistic Digital Mouse Whole-Body
MRTDosimetry	Metrology for Clinical Implementation of Dosimetry in Molecular Radiotherapy
n.c.a.	Non-carrier-added
NA	Networking Activity
NEMA	National Electrical Manufacturers Association
NMI	National Metrology Institute
NOAEL	No Observed Adverse Effect Level
OECD	Organization for Economic Co-operation and Development
PC	Paper Chromatography
PET	Positron Emission Tomography
Ph. Eur.	European Pharmacopoeia
PIC/S	Pharmaceutical Inspection Co-operation Scheme (PIC/S)
PL	Package Leaflet
PRISMAP	European Medical Radionuclide Program
QbD	Quality by Design
QC	Quality Control
QM	Quality Management
QMS	Quality Management System

RCP	Radiochemical Purity of Radionuclides
RNP	Radionuclidic Purity
ROBY	Rat Whole-Body
SAMIRA	Strategic Agenda for Medical Ionizing Radiation Applications
SI	International System of Units
SME	Small Medium Enterprise
SmPC	Summary of Product Characteristics
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SOP	Standard Operating Procedure
SPECT	Single Photon Emission Tomography
Sv	Sievert
SWP	Safety Working Party
TAC	Time Activity Curve
TLC	Thin Layer Chromatography
TNA	Transnational Access
USP	The United States Pharmacopeial Convention
WP	Work Package
Zn	Zinc
β	Beta
γ	Gamma

Participant short names

CERN	European organization for nuclear research
NPL	National Physical Laboratory
PSI	Paul Scherrer Institut
CEA	Commissariat à l'énergie atomique et aux énergies alternatives
IST-ID	Associação do Instituto Superior Técnico para a IST-ID Investigação e Desenvolvimento
DTU	Danmarks Tekniske Universitet
CHUV	Centre hospitalier universitaire vaudois
GANIL	Grand Accélérateur National d'Ions Lourds
SCK CEN	Studiecentrum voor Kernenergie / Centre d'étude de l'énergie nucléaire
ARRONAX	Groupement d'intérêt public ARRONAX
ESS	European spallation source ERIC
TUM	Klinikum rechts der Isar der technischen Universität München

KULeuven	**Katholieke Universiteit Leuven**
MedAustron	**Entwicklungs- und Betriebsgesellschaft MedAustron GmbH**
SCIPROM	**SCIPROM Sàrl**
MUI	**Medizinische Universität Innsbruck**
ILL	**Institut Max von Laue - Paul Langevin**
JRC	**JRC -Joint Research Centre- European Commission**
NCBJ	**Narodowe Centrum Badań Jądrowych**
GSI	**GSI Helmholtzzentrum für Schwerionenforschung GmbH**
LU	**Latvijas Universitāte**
INFN	**Istituto Nazionale di Fisica Nucleare**
UiO	**Universitetet i Oslo**

List of Figures

List of Tables

Summary

Radiopharmaceuticals are considered Medicinal Products, thereby they must be prepared and applied within the regulated area of pharmaceuticals. This includes radionuclides, which have seen extraordinary advancements in research and development over the last decade in regards to theranostics. The governing EU directives and regulations, including regulatory guidance, cannot keep pace with this development. PRISMAP, the European Medical Radionuclide Program, brings together key nuclear research centres and leading clinical translational research facilities across Europe to provide a sustainable source of high purity grade new radionuclides for the starting research community. One of PRISMAP`s paramount aims is to standardise and harmonise research and development activities with novel radionuclides to cope with pharmaceutical regulatory requirements and provide guidance for clinical translation. The PRISMAP workshop: "Radionuclide Production to Nuclear Medicine Clinical Applications: Regulatory Standards and Harmonisation of Quality and Safety", held in February 2022, provided the basis for this document, which gives guidance for the early phase clinical research with novel radionuclides. It describes the current standards and a harmonised view of the European regulatory framework. The document complements the existing regulatory framework and is not considered legally binding.

Six chapters cover different aspects in radiopharmaceutical development. Each chapter includes dedicated guidelines and guidance documents from regulatory authorities and professional organisations, as well as references to scientific publications on the respective topic.

An **introduction** of PRISMAP and the project scope is followed by a definition of **terms and nomenclature** for specification of novel radionuclides within PRISMAP. The following chapter focuses on the **production of radionuclides** and implementation of **GMP** in the radiopharmaceutical development process. It provides relevant definitions and gives recommendations where GMP compliant processes should be introduced in the production of novel radionuclides. Guidance for controls of radionuclides including starting materials, process validation, in-process controls, chemical precursors and production of radiopharmaceuticals are briefly addressed. The subsequent chapter covers **quality specifications and quality control**. It includes details on relevant European Pharmacopoeia texts and guidance for compliance, summarises other regulatory texts from the EMA and ICH, giving general considerations on specifications and specific guidance for validation of analytical methods. It provides definitions on drug substance and drug product and addresses all relevant specific quality criteria for novel radionuclides. The next chapter deals with **metrology and medical physics aspects** in clinical translation. The relation to the Basic Safety Standards of the Council Directive 2013/59/Euratom is described, which includes aspects of therapy planning and dosimetry for novel radionuclides. Standardisation in relation to traceability is addressed in a dedicated part on Metrology. The role of Medical Physics in the context of standardisation and harmonisation of the clinical use of novel radionuclides for imaging equipment, image acquisition, processing parameters, and quality control implementation of new technologies is summarised.

The final chapter covers **Non-Clinical Safety and Pharmacology** aspects and provides an overview of the current guidance documents to assess preclinical dosimetry, toxicity (new EMA guideline specific for radiopharmaceuticals), and pharmacology of radiopharmaceuticals, which are developed with the aim to be used in human clinical trials. Recent specific guidance documents on this topic, particularly from the IAEA are summarised and included.

This guidance document serves as an essential and comprehensive guide for radionuclide producers, radiopharmaceutical translational scientists, clinical and hospital based radiopharmaceutical development researchers through the complex jungle of pharmaceutical regulations and guidelines. It provides a harmonised view to standardise data required for clinical translation of novel radionuclides.

1. Introduction

1.1 Standardisation and harmonisation within PRISMAP

PRISMAP`s main goal is to provide a sustainable source of high purity grade new radionuclides for nuclear medicine, involving from the onset upcoming major European infrastructures, to provide a single-entry point for all researchers active in this field including; SMEs, global pharma, nuclear centres, hospitals and universities, using standardised access procedures. PRISMAP thus strives to create a paradigm shift in the early phase research on radiopharmaceuticals, targeted drugs for cancer – one of the major diseases in Europe – theranostics and personalised medicine, shaping the European medical radionuclide landmark as a gold standard to accelerate the applications of novel radionuclides and the development of novel radiopharmaceuticals, thereby ultimately leading to better healthcare for the improvement of our citizens' life.

To reach the final goal of clinical application of emerging medical radionuclides, already at early stages of development, the pharmaceutical regulatory environment for the translational process from basic research to clinical application must be considered. Therefore, the PRISMAP consortium had to find consensus defining common pharmaceutical standards applicable for all production (WP2-TNA2) and translational research activities (WP3-TNA3) considering the existing quality frameworks such as Good Manufacturing Practices (GMP), European Pharmacopoeia and Good Laboratory Practices (GLP). This activity led by MUI, is the main goal of WP4, NA1 "Harmonisation and Standardisation" within PRISMAP. This WP is composed of radionuclide producers (WP2-TNA2: ARRONAX, CERN, ILL, SCK CEN, NCBJ, PSI, DTU, JRC), translational research hubs for preclinical and clinical studies (WP3-TNA3: CHUV, TUM, NCBJ, SCK CEN), and KULeuven in relation to radionuclide metrology and calibration standardisation of clinical equipment.

1.2 Scope of deliverable 4.1

The overall scope of this document is to provide harmonised standards for production of radionuclides and generation of data in radiopharmaceutical research suitable for clinical translation. In the very initial phase of the project the potential pathways for clinical translation were discussed and the specific scope clearly defined. The Pharmaceutical Directive 2001/83 EC, but also pharmaceutical legislation in non-EU members in Europe, unequivocally defines radiopharmaceuticals as Medicinal Products, independently of the radionuclide used or the potential application (diagnostic or therapeutic). For final routine clinical use based on Marketing Authorization of these products clinical trials have to be conducted, which have to follow the new Clinical Trial Regulation (Regulation (EU) No 536/2014) within the EU. Many recent developments in radiopharmaceuticals, particularly related to theranostics, were initially clinically applied outside clinical trials, based on certain national pathways (1) and typically direct preparation of radiopharmaceuticals within hospitals (2). This document only refers to processes of clinical translation following the Clinical Trials Regulation or respective legislation in non-EU member-states, as for national pathways often no clear regulatory framework exists. However, even if the clinical application of novel radiopharmaceuticals may not necessarily follow this legislation, it should be stressed that the basic principles to ensure the quality and safety of novel radionuclides and radiopharmaceuticals, described herein, have to be followed independently of the legal framework applied. This is also true for users outside Europe, where regulatory standards may be different (3,4). Therefore, this document provides guidance for the whole PRISMAP Consortium and Users of PRISMAP`s services in the way to accelerate the applications of novel radionuclides and development of novel radiopharmaceuticals, without impairing quality and safety.

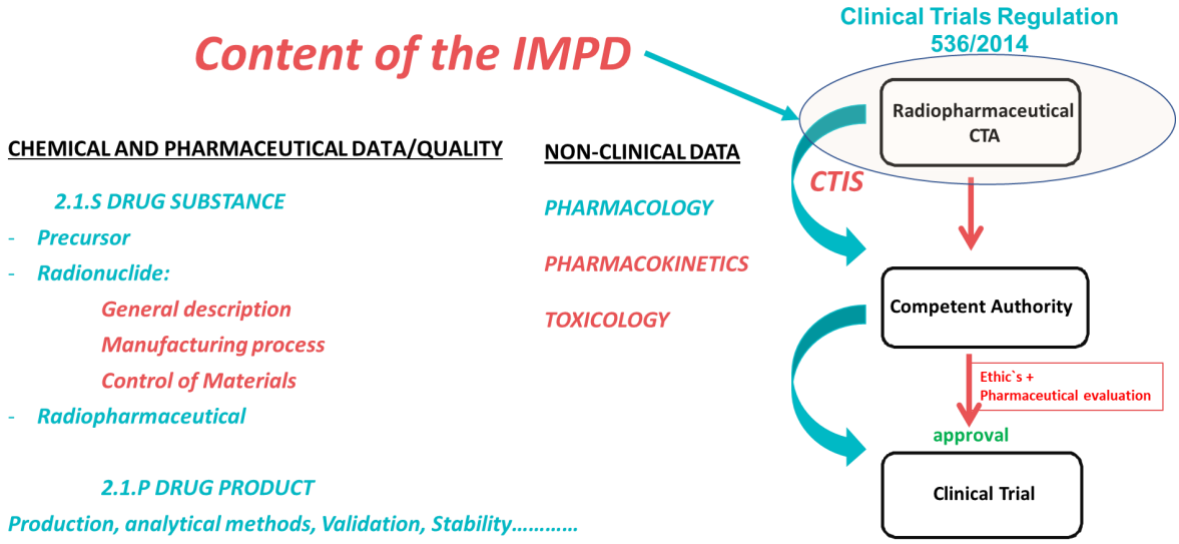

Figure 1. Main content of an Investigational Medicinal Product Dossier (IMPD) with major parameters related to novel radionuclides (left). Clinical Trial application (CTA) and approval process involving radiopharmaceuticals according to the Clinical Trials regulation (right, modified from (1))

The application process for a clinical trial in Europe following the new Clinical Trial Regulation (Regulation (EU) No 536/2014) is outlined in Figure 1. The clinical trial application must include detailed documentation on the novel radiopharmaceuticals in a so-called Investigational Medicinal Product Dossier (IMPD). The IMPD structures the information of a Medicinal Product into data related to the chemical and pharmaceutical quality and to safety and efficacy, in case of a first in-human application mainly non-clinical data. For chemical and pharmaceutical data a dedicated, recently updated IMPD-guideline from EMA is available. Therefore, in the process of developing new radiopharmaceuticals it should be considered that data generation either falls in the category of "quality data" or into "safety and efficacy data", in some cases they may serve both aims. Figure 2 outlines the steps in radiopharmaceutical development and to which category the data can be related to. In general, the pharmaceutical regulatory area defines "quality frameworks" or "good practices" which should be considered in the clinical translation process.

Medicinal products in general are highly regulated. There are many legal texts and guidelines from different legal players providing requirements and guidance for the development and evaluation of new drugs. However, particularly for radiopharmaceuticals, dedicated regulatory guidance is scarce and often general documents must be interpreted to meet the technical requirements for radionuclides and radiopharmaceuticals. As a result, the interpretation by pharmaceutical assessors in regulatory authorities is often a case-by-case scenario. Therefore, absolute guidance and legally based standardisation for novel radionuclides and radiopharmaceuticals is not possible, and this document can only provide general guidance and recommendations for users.

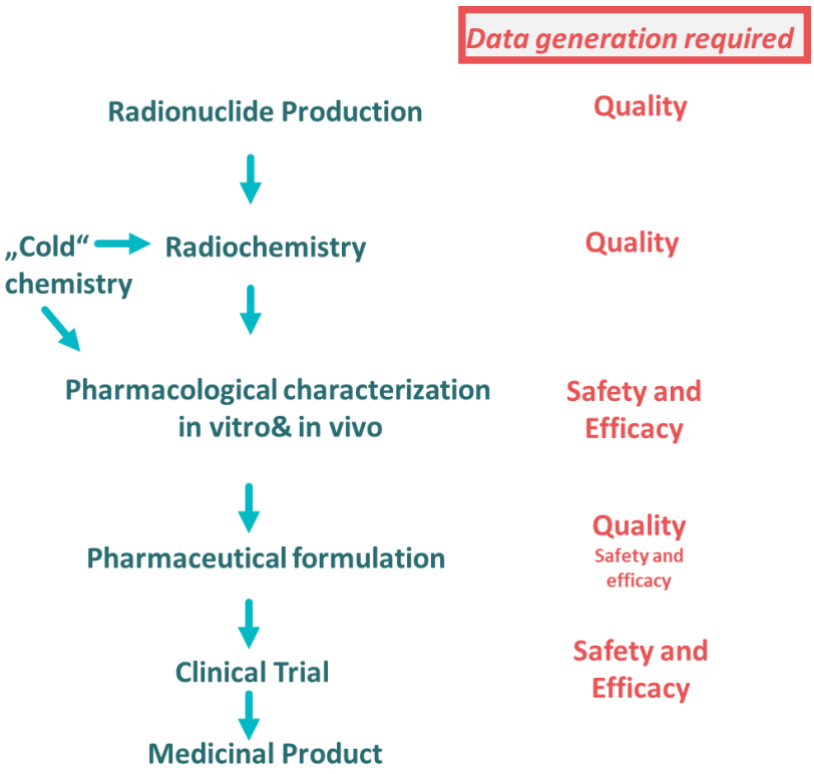

Figure 2. Pathway in the translation of novel radionuclides (left) requires generation of data related to quality or safety and efficacy (middle). Data generation must consider different quality frameworks, when it comes to clinical application, as defined in pharmaceutical regulatory texts, so called "Good Practices"

1.3 Workshop and deliverable Structure

To provide an appropriate interpretation of the current pharmaceutical framework in Europe, WP4 organised a workshop entitled "Regulatory standards and harmonisation of quality and safety", which was held as an online event from February 8th – 10th 2022 with the intent to bring together different experts from regulatory authorities, radionuclide production, radiopharmaceutical research, industry and professional organisations. Representatives of regulatory authorities included EMA, EDQM and National Drug Authorities. PRISMAP members embodied the technical expertise of radionuclide production and radiopharmaceutical research and were complemented with colleagues from the US and Japan. The industrial perspective of radionuclide production and radiopharmaceutical development were presented by two members of the PRISMAP industrial board and professional organisation representatives from the EANM and IAEA provided insight on their activities related to radiopharmaceutical development and regulatory framework from different perspectives.

This workshop provided the major input for this deliverable on Standards and Harmonisation of novel Radionuclides, which is structured in 5 topical domains, partly related to the data requirements from the regulatory authority perspective (in particular the IMPD format):

- Terms and nomenclature used in specification of PRISMAP radionuclides
- Quality – Production and GMP
- Quality – Specifications and quality Control
- Metrology and medical physics for the support of clinical translation of novel radionuclides and radiopharmaceuticals
- Non-clinical safety & pharmacology

These topics are covered in the following chapters and provide PRISMAP`s guidance for standardisation in clinical translation of novel radionuclides and radiopharmaceuticals developed thereof. As the focus of

PRISMAP lies in the application of novel radionuclides, in particular the topics related to quality are focussed on the radionuclides themselves, as the radiopharmaceuticals developed may have a broad variety of properties and may fall under very different classes of compounds, which may require a dedicated focus. For the sake of harmonisation, it is recommended to develop monographs for the individual new radionuclides in the further course of PRISMAP, which eventually could be adopted by the European Pharmacopoeia.

2. Harmonisation of terms and nomenclature used in specification of PRISMAP radionuclides

The following statements are the basis to harmonise the terminology used for the radionuclides within the PRISMAP activities and provide an appropriate nomenclature related to the specific properties of novel radionuclides.

1) The word “radionuclide” should be used instead of “radioisotope”
2) The term “molar activity” should be used instead of “specific activity”. If deemed helpful, the historical term “specific activity” can be added in parentheses.
3) Molar activity should be specified on our web site specifications with reference to a time close to time of shipment. The reference time should be chosen to be equal to the reference time for the activity.
4) For a given batch, the molar activity should be expressed with reference to the time of its determination and stated in this form on the Certificate of Analysis (CoA).
5) In the web site specifications of our radionuclides (from a given producer facility) can be designated as:
   - **Non-carrier-added (n.c.a.), or**
   - **Carrier-added (c.a.), or**
   - **Mass separated**
6) Radionuclides can be specified as delivered in **solution**, in **dry** form or implanted in a **foil**.
7) Wherever possible, the above three designations should be stated with the molar activity and its fractional percentage of the theoretical maximal molar activity.
8) When the radionuclide is delivered in solution, a typical value for the **radioactivity concentration** can be stated in the web specifications and the actual value for a given batch on the Certificate of Analysis (CoA). The nature of the solvent should be stated. The term “specific activity” must not be used to designate activity concentration.
9) The **radionuclidic purity** (RNP) should be stated as a number (percentage) and, where possible, completed with a list of known radionuclidic impurities, together with a numerical expression of the (maximum) fractional content of each impurity as part of the total activity.
10) The RNP and the impurities should be stated with reference to a time close to time of shipment, equal to the time when activity and molar activity are specified.
11) For a given batch, the RNP and the known **radionuclidic impurities** should be stated with the respective reference **time (see point 3)** and included in this CoA.
12) In the specifications name the **expected chemical form** of the radionuclide (stating for example ionic form and solvent). For mass separated radionuclides, the term “implanted in gold” or equivalent can be used.
13) A possible fractional chemical speciation (the radiochemical purity of the radionuclide) shall not be stated.
14) Where possible, important **chemical impurities** (as for example residual target material or transition metal impurities) can be stated as either molar concentration or in ppm (or equivalent).
15) The “**apparent molar activity**” can be included in the specification and on the CoA, but then always with reference to a specific binding system and set of labelling conditions.

3. Quality – Production and GMP

3.1 General remarks

This chapter focusses on the aspects related to production of novel radionuclides, regarding Good Manufacturing Practices (GMP). The production of radiopharmaceuticals themselves and non-radioactive precursors are only briefly addressed in major aspects related to the PRISMAP goals. The topic of quality and specifications is covered in a separate chapter, even though it should be stressed that there is a strong link between quality of a radionuclide and the production process requirements.

3.1.1 GMP requirements for radiopharmaceuticals and clinical trials

In general, the production of routine medicinal products holding a marketing authorization is required to follow GMP as defined in the Pharmaceutical Directive 2001/83EC. GMP requires a Manufacturing Authorization, which is granted by a national competent authority (requirements may differ between countries). The GMP guidelines for the European Union are outlined in Eudralex Vol.4. These general GMP guidelines are divided into four parts (3 basic requirements and related documents) and 19 annexes. There are no specific GMP documents for radionuclides, but a specific annex (Annex 3) for radiopharmaceuticals. It should be considered that aspects of other annexes and texts may apply. Preclinical studies (*in vitro, in vivo*) do not require GMP grade radiopharmaceuticals but GMP in principle is applicable for Investigational Medicinal Products (IMPs) in clinical trials, which are covered in the Clinical Trials Regulation (EU) No 536/2014. A dedicated Annex 13 in GMP deals with specific requirements in clinical trials, this has come into effect in January 2022. This new regulation, however, specifically exempts radiopharmaceuticals for diagnostic applications from the requirements to comply with GMP and manufacturing authorization. As the new regulation has just come into effect, the consequences of this new legislation cannot be predicted and may vary in different EU member states. A detailed discussion on the impact of these changes, potential national differences and relevance for therapeutic radiopharmaceuticals has been published over the last years (5,6).

This reflects the current situation in many European countries, where radiopharmaceuticals are prepared locally and used in-house without the requirement for a manufacturing authorization, which is connected with GMP compliance. This is a strong segment in Nuclear Medicine practice and has been utilised for widespread use of recently developed radiopharmaceuticals for theranostics, being strongly supported by EANM (7,8).

To provide harmonisation and specific standards for this radiopharmaceutical preparation dedicated guidelines have been released by EANM (Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals)(9), and by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) has released a guideline for healthcare establishments with a dedicated annex 3 for radiopharmaceuticals.. Also the European Pharmacopoeia has published a dedicated chapter on the Extemporaneous Preparation of Radiopharmaceuticals (10) to address this specific practice, which may also provide guidance in the use of novel radionuclides within PRISMAP.

More details on these topics can be found in review papers on regulations of radiopharmaceutical practice in general (11) or on the translation of novel radiopharmaceuticals in the European regulatory environment (1,12).

3.1.2 Regulatory definitions and radionuclides

Radionuclides used for radiolabelling, such as those provided within PRISMAP may be viewed differently from a regulatory perspective. The pharmaceutical Directive 2001/83 on page 12, has a definition of a "radionuclide precursor", besides the definition of radiopharmaceuticals, radionuclide generators and kits. This was intended to enable the routine preparation of radiopharmaceuticals by locally combining a commercially available radionuclide precursor (or a radionuclide from a radionuclide generator) with a kit,

resulting in the formation of the final radiopharmaceutical ready for administration without requirement of the framework for pharmaceutical manufacturing. The radionuclide precursor and the kit require a marketing authorization for this routine practice.

A different situation arises when the radionuclide is used within a more complex preparation process. In such a case, it may not be defined legally as a radionuclide precursor. It is generally accepted that not all steps in the production of the radionuclide itself must be covered by GMP. Considerations also have to be made in the definition of the radionuclide that is produced and if it is considered a finished radiopharmaceutical (drug product), an Active Pharmaceutical Ingredient (API) or an API starting material.

The definition of these terms can be found below. More on these definitions and their relevance in the context of novel radionuclides and complex radiopharmaceutical preparations thereof can be found here (13,14).

Definitions of terms relevant in the production of radionuclides

from Directive 2001/83 EC

- *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

Other:

- *Drug substance or active substance:* Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. From a regulatory perspective a Drug Substance is an API that is used for manufacturing a Drug Product.
- *Active Pharmaceutical Ingredient (API)*: : An API is a drug substance in GMP grade. Typical API are: a GMP grade purified radionuclide solution, a GMP grade non-radioactive precursor, a labelled molecule in GMP grade. It is the “regulated” form of an active substance.
- *API starting material*: Precursor of an API. An API starting material does not need to be in GMP grade. Typical API starting materials are: the target material, an irradiated target (or implantation foils implanted at MEDICIS), a purified radionuclide solution, a chemical precursor for radiopharmaceutical preparation.
- *Drug product (medicinal product):* A formulated product manufactured with the combination of drug substance (APIs) and excipient as applicable.
- *Medical device:* see REGULATION (EU) 2017/745 (applicable e.g. for microspheres intended for intra-arterial therapy)

3.2 Production of radionuclides

3.2.1 Types and considerations

General routes of manufacturing radionuclides for use in radiopharmaceutical preparations are:

- Nuclear fission produced radionuclides. Fission always produces a large diversity of radionuclides. Therefore, radionuclides produced from such a process must be carefully controlled in order to assure radionuclidic purity.
- Charged particle induced reactions: radionuclides may be produced by irradiating target materials with charged particles (protons, deuterons, alphas, etc.) in particle accelerators such as cyclotrons. The desired nuclear reaction will be influenced by the energy of the incident particle, the target thickness and the radionuclidic composition after irradiation will depend on the duration of irradiation , cool down time and the isotopic composition and chemical purity of the target material.
- Neutron induced reactions: radionuclides may be produced by irradiating target materials with neutrons of different energies in nuclear reactors or other neutron sources. The desired nuclear reaction will be influenced by the energy spectrum of the neutron flux and the radionuclidic composition after irradiation will also depend on the duration of irradiation and isotopic composition and chemical purity of the target material.
- Radionuclide generator systems: Radionuclides of short half-life may be produced by means of a radionuclide generator system involving separation of the daughter radionuclide from a longer-lived parent by chemical or physical separation.

3.2.2 Introduction of GMP during the production process of a radionuclide

In any production of a Medicinal Product, the quality framework of GMP is introduced at a certain step of the manufacturing process. For the production of radionuclides, it has been clearly recognized that not all steps can be covered by GMP. The following Table 1 can be found in the European GMP guidelines Eudralex vol. 4 annex 3, page 3.

Table 1. GMP coverage in the process of manufacturing of radiopharmaceuticals (from (15))

Type of manufacture	*Non - GMP **	*GMP part II & I (Increasing) including relevant annexes*			
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	*Reactor/Cyclotron Production*	*Chemical synthesis*	*Purification steps*	*Processing, formulation and dispensing*	*Aseptic or final sterilization*
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.*

Notably, Annex 3 differentiates the requirements of these steps for the radionuclide manufacture, which are directly carried out at a nuclear reactor or cyclotron (which can generally be described as “irradiation”) from those which are related to the processing of radionuclides. While it is acceptable that “irradiation” is non-GMP, the processing part should be covered by GMP. Annex 3 states that it is applicable to manufacturing procedures employed by industrial manufacturers, nuclear centres/Institutes and PET centres for the production of and quality control for (finished) radiopharmaceuticals, PET radiopharmaceuticals, radioactive precursors for radiopharmaceuticals production and radionuclide generators. It must be stressed that radiation protection must remain a priority in all processes. There has been a debate whether the term industrial manufacturing excludes local, in- house production processes (8), national differences exist in this interpretation. Also, for mass separation processes and processes combined with mass separation, no guidelines are available and it remains a matter of interpretation where GMP compliance needs to be covered but it is evident that mass separation is technologically very similar to cyclotrons, hence a

classification similar to the latter (i.e. non-GMP) is clearly indicated. PRISMAP intends to be involved in setting up the standards together with the competent authorities.

Two scenarios can be considered in relation to GMP compliance, depending on the product type:

1) Radionuclide defined as a drug product:

If the radionuclide is regarded as a finished product (a "radionuclide precursor"), then EudraLex Vol. 4 Part I applies. The steps after radionuclide production (e.g. after leaving the cyclotron or reactor facility) then have to comply with GMP. This includes the radiochemical separation processes and possibly chemical synthesis steps involved as well as steps for final formulation and dispensing, and (if applicable) sterilisation. It is important to note, that the target/ starting materials may not meet full GMP compatibility but should satisfy certain quality requirements (see chapter 4).

This way is, of course, preferred by regulatory authorities, as there is direct oversight by pharmaceutical inspectors over the radionuclide production process with GMP compatibility. The Marketing Authorisation holder of the radionuclide precursor is then also responsible for quality and release by a qualified person and may not necessarily have to disclose all information of the production process and quality controls to the user, but may make this accessible for the regulatory authorities only. This pathway certainly is also mandatory for commercial producers, as in case of routine use marketing authorization as a radionuclide precursor can be approached, which then allows commercial distribution to any clinical user.

2) The radionuclide is considered as an API:

If the radionuclide is considered as drug substance or API, EudraLex Vol. 4 Part II on Production of API`s applies. Application of GMP is outlined in Table 2 of this document.

Table 2. GMP coverage in the process of manufacturing of an API (extract from Eudralex Volume 4, part II, page 7)

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

Thereby GMP does not apply for production of the API starting material but applies to all of the following steps. The process of nuclear transformations is not listed and therefore supports exclusion from GMP requirements. This allows a producer to provide a radionuclide from a non-fully GMP compliant process to a producer of a radiopharmaceutical. This entity with a licence to produce radiopharmaceuticals then can transform the delivered API starting material into an API by

- defining specifications,
- defining quality control tests (own or contracted to a GLP or GMP-laboratory)
- and possibly - own processing before it enters the API manufacturing step.
- Knowledge about potential impurities is required and a risk analysis should be provided by the producer of the API starting material.

This requires the responsible person producing the radiopharmaceutical to test every incoming batch of a radionuclide to ensure API quality and holds responsibility for the quality of the radionuclide.

Options of potential declarations as API versus API starting material (of radionuclides and other materials required) are summarised in the following Table 3.

Table 3. Potential options of declaration of the radionuclide and materials used in the preparation as API or API starting material

API starting material	API
Target material	Purified radionuclide solution
Irradiated target material	Chemical precursor for radiolabelling (if not removed in the production process)
Radionuclide on solid support (foil)	Radiolabelled molecule
(purified) radionuclide solution	
Chemical precursor (removed in the production process)	

This process allows the introduction of novel radionuclides into a clinical application from a process that must be performed in a facility that cannot qualify as a pharmaceutical producer. This is, of course, of utmost importance within PRISMAP where several production routes (e.g. including mass separation) cannot be performed under GMP conditions. Such a process has allowed for the introduction of novel radionuclides, such as Ac-225, into a GMP compliant process for clinical application (16).

In any case, the manufacturer of the final radiopharmaceutical should describe and justify the steps for manufacturing of the active substance and the final medicinal product, whereby GMP (part I or II) applies for the specific process/manufacturing steps, which is clearly stated in Annex 3.

3.2.3 Description of the manufacturing process and process controls

In general, the production process of new radionuclides in PRISMAP should be fully documented and traceable. Specifications should be provided along with the product. Even if the radionuclide is considered as an API starting material or intermediate, the radionuclide production process should be fully documented and transparent. It is recommended to provide a schematic presentation of the radionuclide production process, an example, how this can be presented is shown in Figure 3.

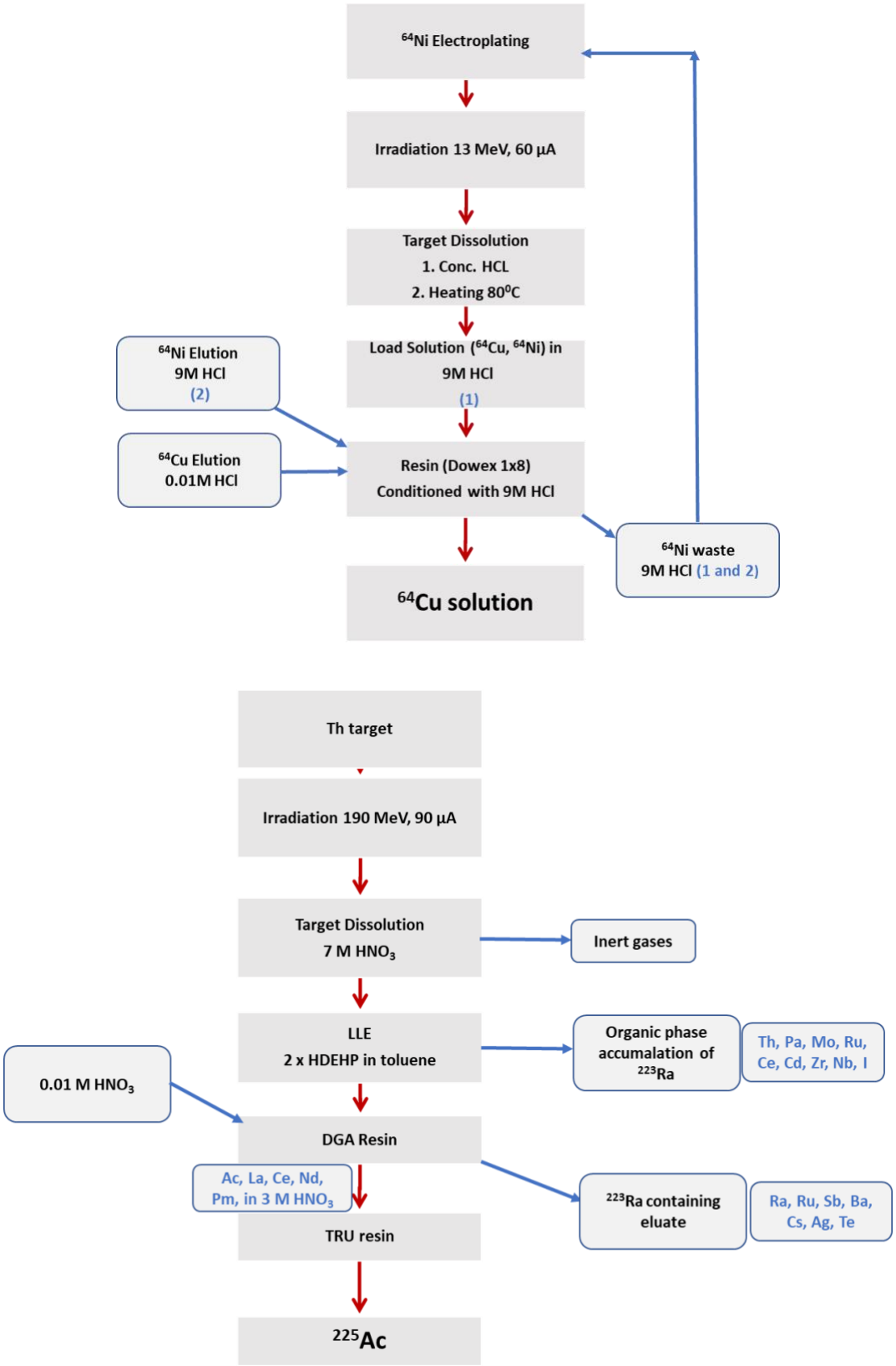

Figure 3. Schematic presentation of a production process exemplified for a typical Cu-64 manufacturing and Ac-225 wet chemistry. Please note that the actual production process can be technically different, the scheme serves as a template.

The activity with calibration time should be provided together with the batch formulation, radionuclidic purity, and radiochemical purity, if technically possible. The molar activity (specific activity) and apparent molar activity (if relevant for the intended use) are also recommended to state. A more detailed summary of requirements can be found in (17), specifications are addressed in more detail in chapter 4.

The producer of a radionuclide as an API starting material should provide a risk analysis about the potential impurities in the API starting material. Examples of an advantageous settings for external irradiation processes minimising risks are summarised below:

- the target is a closed system of inert materials (filled quartz ampoule)
- The target enclosure (e.g. quartz ampoule) is cleaned, filled and closed by the radionuclide manufacturer within a well monitored and documented process
- the target filling material is well characterised (enrichment, impurities, stability)
- the target is irradiated under well-defined conditions

The nuclear reactions, as well as, some possible undesired nuclear reactions should be described and the irradiation conditions should be given (MA/CHMP/QWP/545525/2017 Rev. 2). The further downstream part of the manufacturing process will comply with GMP requirements, Eudralex Vol. 4 part II and Annex 3. Additional tests such as bacterial endotoxins and sterility tests become mandatory. For API as pharmaceutical grade products also the requirements for primary packaging (primary packaging refers to the materials that make direct physical contact with your product) are regulated and specifically addressed in the pharmacopoeia. Based on the Ph. Eur. monographs about ^{177}Lu and ^{90}Y (Ph. Eur. monographs No.1798 and 2803) , the radionuclides produced as API should be submitted with the following controls: pH, radionuclide identification, chemical impurities, radionuclidic purity, radiochemical purity, bacterial endotoxins, and sterility, which will be addressed in the following chapter 4.

3.2.4 Controls of critical steps and intermediates

In case of critical steps in the synthesis, tests and acceptance criteria for their control should be briefly summarised (EMA/CHMP/QWP/545525/2017 recommendations for investigational medicinal products, IMPs in clinical trials). The process controls can e.g. include radiation monitoring of a process, activity probes in modules, filter testing etc. In general, all the steps of the production procedure should be traceable. For reactor targets, a possible external contamination of the quartz ampoules should be considered. This can be dealt with either by a dedicated washing process or via the subsequent chemical separation and QC respectively. The selection of controls should then be discussed in a risk assessment.

3.2.5 Control of starting materials (target material)

The target material should be as pure as necessary to avoid the production of unwanted radioactive impurities or deviations in the mass-separation process, especially long-lived radionuclides and radionuclides posing dosimetry problems in the final radionuclide product. Purification of the target material prior to preparing the target may be necessary. As an example (for no-carrier-added processes), an enriched element used as target material may be contaminated with a small amount of an undesirable nuclide of the same element or another element, which will remain in the target and/or can be activated by the nuclear reaction. If the resulting nuclide belongs to the same element as the radionuclide to be produced this will dramatically lower the molar activity (specific activity) of the produced radionuclide since the radioactive and non-radioactive isotopes of the same element cannot be chemically separated during the purification steps. The enrichment of the target material will need to be specified, along with the proposed radionuclidic contaminants post irradiation/chemical separation. Likewise, the typical thick target composition for mass separated isotopes, which may affect the mass separation process, should be stated.

It would be prudent to control the target material in use by recording its batch/lot number, have a record of its Certificate of Analysis and, if possible, to create an in-house batch/target number as well an expiration date.

3.2.6 Process Validation

Before including data on the radionuclide production for IMPD submission, the production of a radionuclide should be verified in technical batches. For process validation, in general, the three consecutive batches produced should include: batch records, all the critical steps, the analytical methods (validated or Ph.Eur. compliant), sterility and stability studies. More details on general issues related to process validation involving radiopharmaceuticals can be found in a recent EANM guideline (18).

3.2.7 Batch formula

The batch formula of a radionuclide should contain all components (including excipients) and quantities, including e.g. concentration (activity and volume), radionuclidic purity, chemical impurities.

3.3 Chemical precursor and production of radiopharmaceuticals

3.3.1 Chemical precursors for clinical trials

There are two types of radiopharmaceutical precursors [4]. A radionuclide precursor is a radionuclide produced for radiolabelling of another substance prior to administration as outlined above. Chemical precursors (for radiopharmaceutical preparations) are “non-radioactive substances obtained by chemical synthesis for combination with a radionuclide” as defined in a general monograph of the European Pharmacopoeia (No2902), whereas this term is not defined in the pharmaceutical directive or related legal texts.

In likeness to radionuclides as API or API starting material, if the chemical precursor is considered as an API, it must be produced under GMP, therefore final quality control requirements may be reduced. In the case where the chemical precursor, which is not bound to the radionuclide, is removed in the radiopharmaceutical preparation process (e.g. by HPLC separation), the chemical precursor may be considered as an API starting material. Thereby, this API starting material may be used in non-GMP quality, however it then requires basic testing to ensure the identity and purity of the final radiolabelled molecule (the API) in the drug product.

3.3.2 Production of radiopharmaceuticals from novel radionuclides

A radiopharmaceutical intended for use in clinical trials is expected to comply with GMP. As outlined at the beginning the new Clinical Trials Regulation (EU) No 536/2014, national legislation may exempt diagnostic radiopharmaceuticals used in clinical trials from the GMP requirements. However, in some countries this has the consequence that for the starting materials more quality assurance measures are needed. Both the radionuclide precursor and chemical precursor, may be requested in GMP quality, which can be challenging with respect to some novel PRISMAP radionuclides.

Therefore, GMP compliant processes should be foreseen when using novel PRISMAP radionuclides. GMP compliance is facilitated by implementing automated processes, although this is not mandatory. EANM issued a specific guideline for good practices involving automated modules (19). Automation should thereby be considered early on in the development of radiopharmaceuticals from novel radionuclides and can be derived from existing, well-established processes and methods (e.g. (20)), in particular when considering radiometals. Examples of automated GMP compliant processes involving PRISMAP radionuclides have been reported e.g. for Ac-225 (21).

3.4 Guidelines

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. EUR-Lex - 32001L0083 - EN - EUR-Lex (europa.eu)
- EudraLex Vol. 4 Part I, Basic Requirements for Medicinal Products: EudraLex - Volume 4 (europa.eu)

- Eudralex Vol. 4 part II, Basic Requirements for Active Substances used as Starting EudraLex - Volume 4 (europa.eu)
- Eudralex Vol. 4 annex 1, Manufacture of Sterile Medicinal products: 2008_11_25_gmp-an1.doc (europa.eu)
- Eudralex Vol. 4 annex 3, Manufacture of Radiopharmaceuticals 2008_11_25_gmp-an1.doc (europa.eu)
- Eudralex Volume 4, annex 13, Detailed Commission guideline of 8 December 2017 on the good manufacturing practice for investigational medicinal products pursuant to the second paragraph of the Article 63(1) of Regulation (EU) No 536/2014 guideline_adopted_1_en_act_part1_v3_0.pdf (europa.eu)
- Requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials- EMA/CHMP/QWP/545525/2017 Rev. 2 Requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials | European Medicines Agency (europa.eu)
- European Pharmacopoeia, monograph No 2902: Chemical Precursors for radiopharmaceutical preparations.
- European Pharmacopoeia, monograph No 0125: Radiopharmaceutical Preparations.
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials EMA/CHMP/QWP/545525/2017 Rev. 2
- EANM- Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals
- European Pharmacopoeia, Extemporaneous Preparation of Radiopharmaceuticals
- Pharmaceutical Inspection Co-operation Scheme (PIC/S), PIC/S GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS

4. Quality – specifications and quality control

4.1 General remarks

4.1.1 Regulatory overview

As outlined above, radiopharmaceuticals are medicinal products, the regulatory view on these products is rather complex. One major reason lies in the fact that the Active Pharmaceutical Ingredient (API) is not available isolated on the shelf but only exists in the formulated product (drug product), i.e. in solution and in minute quantities. Therefore, the closest available precursor, which is isolated in the process, is often considered, and in a regulatory perspective, handled as an API. This is then usually the radionuclide (radionuclide precursor) and the chemical precursor (e.g. peptide with chelator).

Applications for *market authorization* or *clinical trials*, require a product dossier, which has to include the quality description of the drug substance (API) and drug product and it should follow the template provided by ICH / Common Technical Document (CTD), a dedicated guideline laying down the specific requirements for IMPs. The radionuclide and chemical precursor are documented in section 3.2.S (drug substance part), one document for each. The product itself is described in the section 3.2.P.

The focus of this chapter is on the specifications and quality control of radionuclide precursors. Specifications and quality control of radiopharmaceutical preparations are also considered when the quality of the preparation is directly impacted by the quality of the radionuclide precursor.

4.1.2 Pharmacopoeia and radiopharmaceuticals

In the pharmaceutical regulatory environment, the Pharmacopoeia serves as the reference for quality control of medicines. In Europe **the European Pharmacopoeia (Ph.Eur.) provides official standards that are legally binding in European Countries, not only the EU, but e.g. also Switzerland and Norway**. Other compendial standards exist, such as the International Pharmacopoeia or the US-Pharmacopoeia (USP), but are in general less relevant for radiopharmaceuticals and in particular will not be covered within PRISMAP.

Quality of radionuclides for pharmaceutical preparations (i.e. radioactive precursors) should be in compliance with relevant texts from Ph.Eur.

Relevant texts in Ph.Eur are not only monographs on specific products, but also general monographs and chapters. Even if certain parameters are not mentioned in a specific monograph, they still may be applicable when included in a general text. This e.g. may be the case for Endotoxins, if the product is intended for parenteral application. The product must then be tested for endotoxins even if it is not specifically mentioned in the monograph. There are many interrelations, which are described in the "General Notices" of Ph.Eur. It also should be stressed that not all texts are legally binding, this is e.g. true for general chapters, which only become legally binding when cited in a monograph. Also, not all texts within a monograph are binding, e.g. whereas the section on "production" is a requirement (i.e. one can only comply with a monograph when a certain production pathway is followed), the section on "characters" is only descriptive and not binding.

Compliance with Ph.Eur. is also only valid if the product is prepared within "the framework of a suitable quality system", which is typically GMP, but may also be another suitable quality assurance system (see also Chapter 3).

Table 4 gives an overview of the types of texts and examples for the context of radiopharmaceuticals.

Table 4. Types of Texts in the European Pharmacopoeia

Text	Example	Number	Legally Binding	Content
General notices		10000	Yes	General rules for interpretation of the texts of the European Pharmacopoeia
Specific monographs	Lutetium (^{177}Lu) Solution for radiolabelling	2798	yes	Monograph of a radionuclide precursor
Specific monographs	Gallium (^{68}Ga) PSMA-11 injection	3044	yes	Monograph of a finished radiopharmaceutical
Specific monographs	Tetra-O-acetyl-Mannose triflate for radiopharmaceutical preparations	2294	yes	Monograph of a chemical precursor for radiopharmaceutical preparations
General monographs	Radiopharmaceutical Preparations	0125	yes	General requirements for all radiopharmaceuticals (of a given class)
General monographs	Chemical Precursors for radiopharmaceutical preparations	2902	yes	General requirements for all products (of a given class)
General chapters	Liquid Chromatography	20229	(No)	Description of HPLC, as the chapter is typically cited when an HPLC method is described it becomes legally binding
General texts	Extemporaneous Preparation of Radiopharmaceuticals	51900	No	Standards of preparation of radiopharmaceuticals of unlicensed products

In any case, the quality control and definition of specification of novel radionuclides within PRISMAP should follow the scope of existing specific monographs on radionuclides for radiolabelling, general monographs and chapters as applicable and try to achieve Ph.Eur. compliance.

Conditions to achieve Pharmacopoeial compliance for radionuclides

- Qualified/validated processes
  - In order to set quality standards for radionuclides, the irradiation/purification process should be qualified/validated
- Cyclotron/reactor/ mass separation:

  - Quality of target material and target material holder should be assessed and documented.
  - Irradiation (mass-separation if applied) parameters should be defined
- Purification process:
  - Purification process should be qualified/validated.
- All validation and production processes should be documented

For the small-scale production of radiopharmaceutical preparations there is the Pharm. Eur general chapter 5.19. EXTEMPORANEOUS PREPARATION OF RADIOPHARMACEUTICALS. In this text a specific chapter 3-1. deals with the PRODUCTION OF RADIONUCLIDES, that describes the elements that need to be evaluated regarding the efficiency of the production in terms of quality and quantity of the radionuclide produced.

When there is a specific monograph on the Ph.Eur. for a substance/preparation, the monograph is mandatory (both for regulators and for applicants) provided the applicant justifies that the monograph is suitable to control that preparation. All the tests prescribed in a monograph for an active substance or for a finished product should be conducted on a routine basis; periodic testing or skipping of testing has only been authorised in exceptional cases based on sound justifications and suitable experimental development data (Quality by design). The same applies to specifications of active substances and finished products (irrespectively of who conducts the tests). Tests may be performed after the release of the product; this is typically specified in a monograph. If in-house methods are used, they must be validated.

4.1.3 Other regulatory documents related to specifications and quality control

Additionally, to Ph.Eur., other guidelines related to quality should be taken into account.

The ICH provides a series of ICH-Quality guidelines including topics like stability, impurities or analytical procedure development. A dedicated guideline deals with specifications for new drug substances and drug products (ICH Q6A).

An important guideline in the context of quality control and specifications is the Guideline on radiopharmaceuticals from EMA. It provides information based on the structure of the CTD. It is primarily intended as a guidance, which information should be provided for marketing authorization application of radiopharmaceuticals. It is also a useful reference in the clinical development, providing some guidance on specifications, stability testing and controls for radioactive products. However, very little information is provided for radionuclides. In radiopharmaceuticals, the active ingredient finally administered to the patient is a radiolabelled substance (L-X*) that is present in minute amounts and that cannot be isolated and fully characterised and controlled as a pure substance. It is tested in the finished product (identity, purity and assay) but the level of assurance achieved with this testing is lower than in conventional medicinal products. To ascertain the quality of the radiolabelled active substance in the product finally administered to the patient it is the strategy to go back in the process to the closest ‘precursors’ of the radiolabelled active ingredient that can be isolated, characterised and tested: the ligand L and the radionuclide precursor A-X*. These are also the subject of specific Modules 3.2.S on the Drug Substance of the dossier.

Quality Guidelines (e.g. ICH) and recommendations from IAEA and EANM should also be considered, depending on the scale of manufacture (e.g. industrial or hospital) and their scope of application (e.g. clinical trial or compassionate use). IAEA provided a number of publications on specific topics in relation to production and quality control, e.g. outcomes of coordinated research projects on Cu-64 or reports from dedicated meetings (e.g. on Actinium-225), but also more general guidelines on Quality Control of radiopharmaceuticals (22). IAEA also cooperates with WHO on developing quality guidelines for radiopharmaceuticals within the International Pharmacopoeia.

The most important guideline from EANM in this respect is detailed in the next chapter on validation.

4.1.4 Validation of analytical methods

Analytical methods for quality control should be validated to demonstrate that they are suitable for their intended purpose. In Europe analytical methods must be validated **in early phase clinical trials**, which may

not be required in other countries, such as the US. Only methods described in the Pharmacopoeia do not need to be validated, if they are suitable to control the particular material.

Validation of analytical methods is generally described for the pharmaceutical application in

(ICH Q2(R1) HARMONISED TRIPARTITE GUIDELINE VALIDATION OF ANALYTICAL PROCEDURES). Due to the specifics of radiopharmaceuticals and the analytical tests involved, EDQM and EANM developed specific guidance for the validation of analytical methods for radiopharmaceuticals (23) in a concerted effort, elucidating the topic specifically for radioactive materials and preparations. It is an important source to plan the validation of specific tests involving radioactivity. Table 5 provides an extract from this document specifying the need for validation in dependence on the type of analytical method applied.

For the specific instrumentation required for pharmaceutical quality control of radiopharmaceuticals another valuable resource is the Ph. Eur. Monograph 20266 on DETECTION AND MEASUREMENT OF RADIOACTIVITY.

Table 5. Validation of analytical methods for radiopharmaceuticals (from (23))

Type of analytical procedure	Radioactivity Content (assay)	Radionuclide identity (approx. T½)	Radionuclide identity (spectrometry)	Radiochemical identity (HPLC/TLC/PC)	Radionuclidic purity (limit test)	Radionuclidic purity (spectrometry after decay)	Radiochemical purity* (HPLC/TLC/PC)
Characteristics							
Accuracy	+	-	+	+	+	+	+
Precision (repeatability)	+	+	-	-	-	(+)	(+)
Intermediary precision	-	-	-	-	-	(+)	(+)
Specificity	+	+	+	+	+	+	+
Detection limit	-	-	-	-	+	-	-
Quantification limit	-	-	-	-	-	+	+
Linearity	+	+	-	-	-	+	+
Range	+	+	-	-	-	+	+

* - radioenantiomeric purity measurements should be validated analogously

(+) - not always possible (e.g. short half-life, see text)

Furthermore, revalidation may be necessary in the following circumstances:

- changes in the synthesis of the drug substance;
- changes in the composition of the finished product;
- changes in the analytical procedure;

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

4.1.5 Considerations regarding specifications

It is important to remember:

- Quality and specifications alone do not mean anything if not related to safety and efficacy and that quality is more than specifications.
- Explain in a transparent and clear way what you have done and what you are proposing. Justify your decisions/proposals in light of provisions of legal and regulatory requirements and on sound scientific

grounds and always provide relevant supporting experimental results, in-house results or published results

General principles and considerations

- Specification should guarantee the safety for patients at the time of administration and ensure reproducibility and consistency of the production process
- It should be stressed that specifications alone do not mean anything if they are not related to safety and efficacy. It must not necessarily be specified what is technically achievable and it must be transparent to the end-users. Routes of preparation will also influence specifications and methods.
- For radionuclides specifications also ensure appropriate labelling results and must be compatible with the requirements for the user, but also have to consider the needs of the producer for long product shelf life and efficient production.
- Except individual monographs for specific solutions for radiolabelling or radiopharmaceutical preparations, regulatory references do not provide specific requirements. Instead, they state which type of tests should be addressed and some general principles for the justification of proposed limits.
- Specifications must generally include tests for appearance, identity, assay (content or potency) and purity. Specifications for radiopharmaceuticals additionally include: radionuclidic identity and purity, radiochemical identity and purity and, where required, molar activity (specific activity).
- The justification of the specific tests conducted, the impurities limited, and the proposed limits must be made on safety and efficacy grounds and considering the batch results of representative batches manufactured by the proposed method at the proposed site(s) used in pre-clinical and clinical batches and in the validation of the process.
- For Investigational medicinal products the same general principles apply, but the information to be provided should include risk aspects considering the nature of the product, the state of development/clinical phase, patient population, nature and severity of the illness. Available information on comparable products is valuable as supporting information.

Radiochemical and radionuclidic purity

- Radiochemical and radionuclidic purity must be justified on what is known on potential and actual impurities considering the manufacturing process. Available biodistribution data and associated dosimetry risks of these impurities must be considered in the risk assessment.
- If no specific risks are identified and if supported by batch data, RCP above 95% and RNP above 99.9% have usually been considered acceptable.
- Radionuclidic purities between 99.0 and 99.9% could need data and a detailed discussion on the identity of unwanted radionuclides and their impact on dosimetry (biodistribution data could be required).
- Radiochemical purities between 90 and 95% can be acceptable if supported by preclinical studies with such batches. Information on the identity of impurities could be asked for. In addition, sometimes, references to other authorised products can be useful if it is justified that the risk is comparable.

Metallic impurities in radionuclide precursors

- Chemical toxicity of metallic impurities is not expected in most cases (but a brief justification is always valuable and should take into account the ICH Q3D(R1) (Guideline for elemental impurities)).
- Not all ligands are equally sensitive to metal interferences. Considering that the preparation is foreseen to radiolabel several different ligands a conservative approach should be taken to consider all metals that are described in the literature as interfering and set limits for those that could be potentially present considering the quality of raw materials and the purification processes. Alternatively, the determination of the apparent molar activity (AMA) could be implemented (see below)
- During pharmaceutical development it is expected that the applicant demonstrates the efficiency for radiolabelling representative ligands (and, if available, authorised kits). Apparent Molar Activity (AMA) can provide this information on radiolabelling and additionally can serve as surrogate of testing for metal impurities.

4.2 Quality control and specifications of Radionuclides

4.2.1 Identification (2 tests)

The radionuclide of interest should be declared as well as the daughter radionuclides (if applicable); in certain circumstances time of separation of the radionuclides should be declared for the sake of quality control and accuracy of activity measurement.

The radionuclide is generally identified by its half-life or by the nature and energy of its radiation or by both as stated in the monograph. Radionuclidic identity needs to be established - e.g. by γ or β ray spectrometry.

The radionuclide identity test should be performed after appropriate dilution to avoid dead time losses using an ionisation chamber, a Geiger-Müller counter, a scintillation counter or a semiconductor detector. The activity must be sufficiently high to allow detection during several estimated half-lives. The measured half-life should not deviate by more than 5% from the half-life stated in the individual monograph. For the determination of the apparent half-life, which is done before release of the product a deviation of about 10% is typically acceptable.

If needed, the oxidation state as well as the counterion may need to be identified, in particular if it is stated in the name of the product or if it potentially impacts radiolabelling.

4.2.2 Radioactivity

The Ph.Eur gives the following definitions in Monograph No 0125 Radiopharmaceutical preparations:

- Radioactivity: generally, the term 'radioactivity' is used both to describe the phenomenon of radioactive decay and to express the physical quantity of this phenomenon. The radioactivity of a preparation is the number of nuclear disintegrations or transformations per unit time. In the International System (SI), radioactivity is expressed in becquerel (Bq), which is 1 nuclear transformation per second. Absolute radioactivity measurements require a specialised laboratory but identification of radioactivity and quantitative measurement of radioactivity can be carried out relatively by comparing the measured samples with standardised preparations provided by laboratories recognised by the competent authority or by using a calibrated instrument.

In terms of pharmacopoeial compliance the radioactivity in a preparation (radionuclide or radiopharmaceutical), must be stated at a specific time, i.e. the activity reference time (ART). It needs to be ensured that the deviation of the actual activity over the stated radioactivity does not exceed 10%. In particular cases, e.g. therapeutic applications, tighter limits could be foreseen, but may be limited by the accuracy of the measurements.

4.2.3 Molar activity (specific activity)

Molar activity is defined as the activity (in Bq) of the radionuclide of interest per mol of element of this radionuclide present in a preparation. Here all isotopes (stable or radioactive) of this given element are summed. Historically the term "specific activity" was more common which refers to the activity (in Bq) of the radionuclide of interest per gram of element of this radionuclide present in a preparation. In theory a "carrier-free" radionuclide, i.e. without admixture of other isotopes of the same element has the theoretical molar activity of a pure radionuclide). When it decays by decay modes that change the proton number (i.e. electron capture, beta or alpha decay) the daughter nuclide belongs to a different chemical element and the molar activity is not affected by the decay, only the activity, activity concentration and molar concentration decrease over time. However, in practice perfect "carrier-free" radionuclides are rare and a certain decrease of molar activity over time may be observed. If a molar activity (specific activity) is guaranteed this should apply until end of shelf life, or the time clearly be specified when it is applicable.

4.2.4 Radionuclidic purity

- The co-produced radionuclides contained in the final product must be declared

- Radionuclidic purity limits must be set, a typical target radionuclidic purity 99.9%. However, radionuclidic purity limits must be related to radiation dose of impurity, the acceptable additional radiation dose due to the impurity must be justified on a case-by-case basis and may be dependent on the application. In certain cases, the limit is set to ensure that not more than 10% additional radiation dose to the patient results from the impurity.
- The specification of a radionuclidic purity should be valid from the time of release and until the end of shelf life. The producers of the radiopharmaceuticals labelled with the radionuclides must ensure that the limits are met until the end of shelf life of their product.

4.2.5 Radiochemical purity

Radiochemical purity (RCP) of a radionuclide is that percentage of the stated radionuclide that is present in the stated chemical form. As radiochemical purity may change with time, mainly because of radiation decomposition, the result of the radiochemical purity test should be stated at a given date and time. The radiochemical purity limit must be valid at the time of the labelling process. In certain cases, the specification of RCP of the radionuclide is not useful and should be omitted. E.g., radiolanthanides supplied in strongly acidic media will always be in the form of the 3+ ion and determination of pH in these cases also ensures RCP.

4.2.6 pH

The pH is a parameter that needs to be known as it can influence the stability and/or the labelling properties of the radioisotope. In certain cases, pH also supports the identity and purity of the radionuclide (see above). In many cases determination using pH paper is preferred over electrodes for radiation safety consideration, this is also foreseen in many Ph.Eur.monographs.

4.2.7 Metals and metallic impurities

Current Ph. Eur. monographs provide a list of individual metals, each specified with a limit.

E.g. In the monograph on 68Ga, limits are set for Zn and Fe contained in 68Ga-chloride solutions for radiolabelling. The specified elements are selected based on potential impurities (column material/HCl). Limits are often set based on analytical capabilities, not on actual interference with the labelling, which limits the validity of these tests.

Radiopharmaceuticals are exempted from general elemental impurity requirements. However, if there is a toxicological concern of a specific metal, a limit should be set.

There are certain drawbacks of the determination of individual metals and specifying them:

- Not all chelators have the same affinity for these metals, therefore it is difficult to select metals and to define limits
- The cumulative effect of the different metals is not considered.

4.2.8 Apparent Molar Activity (AMA)

An AMA test assesses the effects of all metals on the labelling with a given chelator. If the radiometal solution contains metallic impurities interfering with the radiolabelling by competing for ligand chelating sites, an increased amount of ligand is necessary for complexation of the radiometal. In such a case, the chelation curve would be shifted to the right and a greater quantity of ligand would be required for an equivalent percentage of complexation. This therefore overcomes some disadvantages of the determination of individual metals.

For more technical detail see: Annex 1 of IAEA-TECDOC-1863 Gallium-68 Cyclotron Production

Proposed method:

At a given chelator/ligand concentration and activity of the radiometal, a minimum percentage of labelling is specified. The chelator must be specified, preferably a ligand sensitive to other metallic impurities

Note: the method is under evaluation in the expert group on Radiopharmaceuticals of the EDQM/European Pharmacopoeia and used within a comparative evaluation of PRISMAP radionuclides. PRISMAP will continue to work towards defining where an AMA test is useful to replace or complement determination of individual metals for the novel radionuclides in the project.

4.2.9 Chemical purity

Besides metallic impurities other chemical impurities may have to be considered. Such impurities will depend on the nature of the production process, e.g. using certain solvents in the purification steps or additives in production steps that are of toxicological concern. The pharmacopoeia provides guidance, e.g. with providing limits for residual solvents. In case limits of certain chemical impurities are not described, the limit of an impurity has to be specified in a risk-based approach, taking into account the toxicological profile.

Note: If during validation studies it has been shown that these are consistently much lower than the Pharmacopoeial requirements, testing may be skipped (possibly subject to approval of the competent authorities)

4.2.10 Sterility (Ph.Eur.)

A radioisotope for labelling may need to be sterile. In case sterilisation is not mandatory, control of bioburden should be in place.

Radionuclides MUST be sterile in case of parenteral application if:

- No downstream sterilisation takes place (one-pot chemistry/kit)
- Long shelf life, to prevent microbial proliferation and formation of endotoxins before use

Such radionuclide solutions are sterilised by a suitable method (see Ph.Eur. 5.8 Methods of sterilisation).

4.2.11 Endotoxins (Ph.Eur.)

- The radionuclide for labelling must be tested for endotoxins if no further purification takes place - the limit must allow for endotoxin contribution of other sources (e.g., kits, cassettes)
- Test may be performed post release only in case t½ < 90 minutes

4.3 Radiopharmaceutical (drug product)

Quality considerations of radiopharmaceuticals from novel radionuclides are no different from established radiopharmaceuticals. Specifications for radionuclidic purity should be valid throughout the shelf life of the radionuclide solution which then becomes also the maximum shelf life of the product.

Validation of analytical methods for new radiopharmaceuticals recently has come into focus and has been requested by authorities. Several reports can be found in recent literature (24–29), that also serves as a good example for development and validations of analytical methods to be applied within PRISMAP.

4.4 Starting materials for radionuclide production

4.4.1 Target materials

The composition and purity of the target material, the nature and energy of the incident particle and the duration of irradiation and decay after irradiation will determine the relative percentages of the principal radionuclide and other potential radionuclides (radionuclidic impurities) and thus ultimately the radionuclidic purity. For very short-lived radionuclides including the ones present in most positron emission tomography

tracers (PET) the determination of the chemical state and purity of radionuclide before patient use is difficult. Therefore, before clinical use of these radionuclides, extensive validations and strict operational conditions are essential. Strict control of the range of specified quantity and quality are essential. Any subsequent change in operational conditions should be re-validated. Each batch of target material must be tested and validated in special production runs before its use in routine radionuclide production and manufacture of the preparation, to ensure that under specified conditions, the target yields a radionuclide in the desired quantity and quality.

It is important to stress, that the ultimate radionuclidic purity and molar activity (specific activity) can be impacted by isotopic and chemical impurities of the starting material. However, often the exact relationship between initial impurity and final effect on the produced radionuclide is not necessarily straightforward. It may depend on irradiation conditions (energy spectra, target thickness, duration of irradiation, duration of decay before chemical processing, etc.). In the interest of "robustness of the supply chain" an over-specification of target material properties in regulatory documents should be avoided, else supply issues by a single supplier or irradiator that is capable to match these requirements might put into jeopardy the entire supply chain. Instead of listing exact specifications of qualities that happen to be commercially available today it is generally preferable to provide minimum requirements (higher than, less than) with sufficient margin with respect to presently used qualities. Ultimately it may be better to defer some characteristics to the QC step of the radionuclide rather than specifying the target material.

4.5 Relevant guidelines

- Pharmacopoeial guidelines:
  - European Pharmacopoeia (Ph. Eur.) 10th Edition: Monographs, chapters, general texts
- The International Pharmacopoeia (Ph. Int.) - Radiopharmaceuticals
- ICH guidelines ICH Official web site : ICH
  - ICH / Common Technical Document (CTD)
  - ICH-Quality Guidelines
  - ICH Q6A SPECIFICATIONS: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances
  - ICH Q3D(R1) (Guideline for elemental impurities)
  - ICH Q2(R1) Harmonized tripartive guideline validation of analytical procedures
- EMA guidelines:
  - Guideline on radiopharmaceuticals from EMA
  - Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials
- Professional organisations:
  - IAEA Radioisotopes and Radiopharmaceuticals Reports Copper-64 Radiopharmaceuticals; Production, Quality Control and Clinical Applications
  - IAEA-TECDOC-1863 Gallium-68 Cyclotron Production
  - EANM guideline on the validation of analytical methods for radiopharmaceuticals (2020)

5. Metrology and medical physics for the support of clinical translation of novel radionuclides and radiopharmaceutical

5.1 Introduction

5.1.1 Requirements of medical physics during radiopharmaceutical development

The development of a radiopharmaceutical goes through many phases. First, this kind of research and development is not possible without a sustainable supply of medical radionuclides. Second, there are many

development phases and stakeholders, such as authorities, regulators, suppliers, policies, quality assurance procedures and GMP or safety aspects. Third, a personalised treatment approach and the use of dosimetry techniques contributes to the optimization process of radionuclide therapy, enhanced patient management and the evaluation determination of the patient response. The series of operations that investigate the application of a new radiopharmaceutical, is known as the preclinical and clinical analysis of the activity distribution in vivo, and dosimetry workflow (30). The steps that build up this dosimetry workflow, are

1) the calibration of equipment,
2) performing image acquisitions and activity uptake determination in living organisms,
3) applying data correction and image reconstruction techniques,
4) performing (multimodal) image registration and segmentation,
5) performing time-activity-curve (TAC) analysis and cumulated activity assessment,
6) and calculation of the absorbed dose.

The metrology and medical physics communities are providing improved solutions and better support to complete dosimetry workflow, which is crucial in bringing radionuclide therapy applications to the clinic However, the challenges in the field are huge, such as the application of quantitative imaging, internal dosimetry methods, the development and clinical use of therapy planning software, calibration of radionuclide calibrators and medical imaging equipment, and the installation of advanced quality assurance and quality control procedures. One should as well apply an optimization strategy, as outlined in the Council Directive 2013/59/Euratom of the European Commission.

Given the evolution in the field, we are convinced that the involvement of metrology and medical physics will be an important contribution to the overall process of standardisation and harmonisation. Therefore, it is of no coincidence that the European Commission proposed an action plan to help with the treatment and care of cancer in Europe. This plan is called the Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) (31). The goals of the action plans are to ensure that the diagnostic and therapeutic use of ionising radiation are in line with the highest standards, and important: synergies between disciplines are to be found!

5.1.2 Radionuclide therapy planning

Over the past decades, nuclear medicine has evolved considerably, with a growing interest in the field of theranostics, and with the introduction and application of novel radionuclides for radionuclide therapy (32). This evolution has brought an increased awareness that, with these novel radionuclides, and with the development of new techniques and procedures, this field is progressing towards a more advanced and sophisticated radiotherapy setting. In that context, the experiences that were built up in the past, particularly in the field of external beam radiotherapy and brachytherapy, have shown that performing such an advanced therapy requires a much higher level of multidisciplinary support and organisation along the translational pathway and in the clinical application. For nuclear medicine, this means that at any step along the pathway, and from the production through to the application of radionuclides *in vivo*, traceability and accurate determination of radioactivity will be necessary for investigating the relationship between the radiation-absorbed dose to tissue and the related biological effects. The recommendation to optimise the relationship between tumour control probability and potential complications in normal organs and tissues was explicitly stated by the International Commission on Radiological Protection in Publication 140 (33). It is essential for this optimisation to quantify the radiation dose to both tumours and normal tissues. Multidisciplinary cooperation between all involved areas of expertise towards standardisation and harmonisation in this domain will be crucial for the study of the dose-effect relationships, and for further development of radionuclide therapy in general.

5.1.3 Individual dosimetry requirements

In the context of medical exposures, radionuclide therapy should be patient-specific and optimised with prior treatment planning. This optimization has been formalised in Council Directive 2013/59/Euratom of the European Commission, which outlines the international Basic Safety Standards for protection against the

dangers arising from exposures to ionising radiation. Article 56 of this Council Directive requires 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 optimization that is described in art. 56 of the EU Directive is unconditional, clear, and in practice will have a direct effect to the hospitals that are providing radionuclide therapy to patients (34). Unfortunately, a European survey in 2015 showed that to increase the implementation of individual dose planning and post-treatment verification in nuclear medicine applications much needs to be addressed(35). Therefore, the challenges that lay ahead will require a more systemic involvement of medical physics experts, as concluded in the report form a scientific seminar held in 2019 by the European Commission with a Group of Experts referred to by the Euratom Treaty (36). The involvement of medical physic should occur much earlier in the translational pathway, and preferably from the onset of the development of these novel radiopharmaceuticals.

The EANM recently published a position paper on Article 56 of the Council Directive and recommended three levels for optimization and prescription of radionuclide therapy that should comply with the EU Directive (37). The 3 levels are based on the prescription and reporting levels of absorbed doses in radiotherapy as defined by the International Commission on Radiation Units and Measurements (ICRU).

The levels are:

- Level 1: activity-based prescription and patient-averaged dosimetry
- Level 2: activity-based prescription and patient-specific dosimetry
- Level 3: dosimetry-guided patient-specific prescription and verification

Level 1 should be the minimum requirement, and without that, therapy should not be performed. It is important to guarantee that the appropriate activity is administered for optimized treatment. The EANM emphasises the importance of metrology support in the context of radionuclide therapy. In ICRU Report 96, the commission has progressed further on these levels of prescription, recording, and reporting, and establishment of standardised terminology and nomenclature (38). Recent publications by international authority organisations in radiation protection, such as the ICRP and the ICRU, illustrate the progression that is being made towards advanced radionuclide therapy planning.

5.2 Metrology aspects

5.2.1 Standardization of measurements

Metrology is the domain of expertise that can provide standards, for the measurement of radioactivity and radiation in the field of nuclear medicine. A primary standard in metrology is one that is sufficiently accurate that it is not calibrated by, or subordinate to another standard. The primary and secondary derived standardisations achieved by national metrology institutes (NMIs) are necessary stepping stones for scientific development of nuclear medicine. These standards are internationally compared and verified. They ensure a global harmonisation and equivalency in their use. The importance of international standardisation comparisons has been demonstrated by revisions of standardisations related to commonly used diagnostic and therapeutic radionuclides (39,40). These standards are foundations, and the implications for science, healthcare and economy can be immense when they are being questioned.

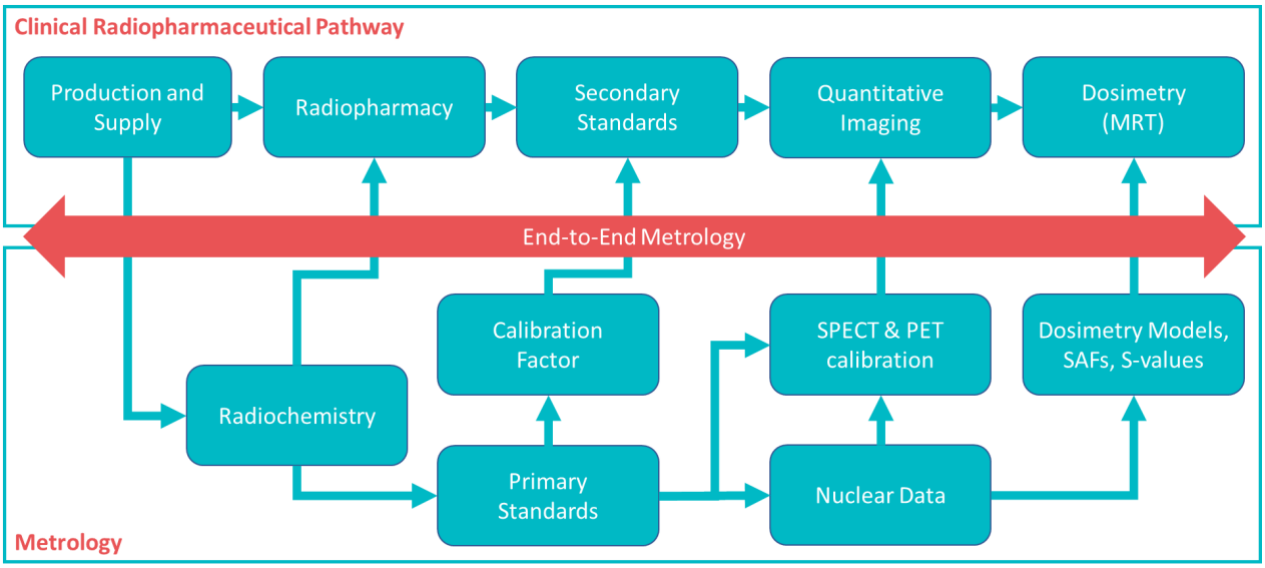

Figure 4. The involvement of metrology in different steps of development and clinical translation of radiopharmaceuticals

5.2.2 Accuracy of equipment

The research performed at NMIs and nuclear physics research laboratories provide physical parameters, such as the half-life, or the branching ratio of a radionuclide for a particular decay mode. It is important that the most recent findings for these physical parameters, and their achieved accuracy, are applied in a consistent manner throughout the field. It is unfortunate that differences are observed in the used branching ratio or half-life of some radionuclides in medical imaging equipment. The manufacturers that are involved in the development of medical imaging equipment and associated software should apply the most up-to-date nuclear data or allow for updates or adjustments when this information becomes available. If not, at least detailed information about the implemented physical parameters should be provided to the end-user community. Traceability of the activity to a primary or secondary standard and correct use of physical quantities are crucial for the development of novel radionuclides in nuclear medicine, and they are very important for the calibration of all the measurement equipment used in preclinical and clinical studies. It is recommended that good communication exists between manufacturers and customers, and that there is sufficient openness during the purchase, the intrinsic use of equipment, and the after sales service. It is also recommended to update nuclear data much faster, especially for novel radionuclides. Working groups dedicated to the application of radionuclide therapy would therefore be very useful at the level of the standardisation organisations, such as the International Organisation for Standardisation (ISO), the International Electrotechnical Commission (IEC), the National Electrical Manufacturers Association (NEMA), and the Bureau International des Poids et Mesures (BIPM).

5.2.3 Traceability from preclinical to clinical applications

Preclinical studies are usually exploratory and investigate the very first use of a novel radionuclide in cells, tissue slices or a living organism. At this stage of the translational pathway, aspects of metrology are mostly absent, and NMIs are rarely involved. Traceability becomes even more important when performing multi-centre clinical studies, which are usually carried out across different countries around the globe. The use of a common standard is the only way of ensuring that the collected data can be combined in a useful manner. The clinical study or trial design should include details and practical implementation strategies for the use of a common standard before the onset of the study. Preclinical investigations and clinical trials should be performed with equipment that has been calibrated. During this early phase of development, experience with techniques and equipment should be built up, so that later use in routine clinical environments is correctly performed and traceable in an equivalent manner.

Applying end-to-end metrology, from the production and supply up to the point of dosimetry, will ensure the highest standards in the field, as mentioned by the SAMIRA action plans. Setting up a primary standard is not cheap, and it is probably the main reason why NMIs have rarely been involved at the start of a novel radiopharmaceutical development. However, it is encouraging to see that this is changing, and radiopharmaceutical research and industry is realising that it should start metrology and all aspects of traceability much earlier in the process. After all, a systematic miscalibration of the equipment or activity should be avoided and could be very detrimental for all subsequent applications (41). Suppliers should provide details about the calibration of the activity, the influence of the shape and material of the used vials or syringes, the exact time-of-separation for parent-progeny radionuclides, etc. (42,43). Traceability is a regulatory issue, but unfortunately, it is usually not a regulatory requirement in most European countries. The use of comparison exercises and (inter)national metrology campaigns for radionuclide calibrators, and the equipment that depends on it, should be part of a good practice strategy (44,45). In that way, NMIs can provide essential services to the broad field of nuclear medicine.

5.2.4 Accuracy in diagnostics vs. therapeutic applications

It is generally accepted that the use of ionising radiation for therapeutic applications should be governed with much more caution than for diagnostic applications (46). The reasons are of course the stochastic and deterministic effects that are expected with diagnostic and therapeutic applications, respectively, and the evidence showing the benefit of individual planning of radionuclide therapy (47).

Authorities have often aimed for a regulatory framework in which a certain accuracy must be achieved. For example, with a maximum allowed deviation of 10% between the prescribed and administered activity, which is the recommendation for reporting at Level 1 by the ICRU (38), which is in line with the pharmaceutical requirements in the European Pharmacopoeia for the declared activity. It is however far from clear whether this accuracy is achieved in clinical routine (41). More research is needed to assess this part of the translational pathway.

5.3 Medical physics support

5.3.1 Standardisation and harmonisation of the use of nuclear medicine imaging equipment

Nuclear medicine imaging equipment, such as gamma cameras, SPECT, PET, and derived hybrid imaging modalities have become sophisticated devices. These devices usually consist of advanced radiation detector technology that is designed to detect emitted or transmitted radiation as efficiently as possible. The acquired data are typically stored in a digital format, and subsequent data processing and image visualisation techniques are applied. Modalities that allow for tomography require additional challenges, such as data correction and image reconstruction techniques. In the end, the modalities provide 3D image representations of the spatial or spatiotemporal distribution of the activity that is measured *in vivo*. This equipment is continuously evolving with the advancement of science and technology. Specific knowledge about the operation and behaviour of these state-of-the-art devices is crucial for the investigation of novel radionuclides that usually come with non-default practice or settings.

There is much room for standardisation and harmonisation of the use of nuclear medicine imaging equipment supplied by different vendors in the field. The instrumentation requires careful installation, thorough acceptance testing and use of a continuous quality assurance program. The devices also require proper (cross) calibration and verification of the implemented system settings within the context of the metrology framework that was addressed in previous sections. Calibration of the measurement system should be performed with a traceability to primary or secondary standards. Only then, a more reliable use of the equipment can make sure that the obtained data of clinical trials are comparable in a useful manner. For these kind of specific tasks with the nuclear medicine imaging or measurement equipment, nuclear medicine services should have the availability of a sufficiently large support group of medical physicists.

5.3.2 The role of the Medical Physicist

Medical physics is the healthcare profession that applies the knowledge and methodologies of physics to all aspects of medicine related to the diagnosis, treatment, and rehabilitation of human disease. The European Federation of Organisations for Medical Physics (EFOMP) helps with the harmonisation and the professional, clinical, and scientific advancement of medical physics. In cooperation with the EANM, and other associations, the EFOMP has been extremely helpful with the training of medical physicists for the application of radionuclide therapy.

The involvement and commitment of medical physicists is mostly found in the hospital environment. Medical physicists usually focus on acceptance testing, quality assurance and quality control of the equipment, device management, problem solving, technology and risk assessment, advanced image processing, software development, performing dosimetry measurements and calculations for diagnostic and therapeutic procedures, education of healthcare professionals and trainees, and innovation. Medical physicists are well trained to bridge between different fields of science. They are very useful for the implementation of principles from physics, engineering, mathematics, and statistics, into clinical applications in medicine, (radio) pharmacy, biomedical and healthcare sciences. In the roadmap of clinical applications, it is therefore recommended to broaden the involvement of medical physicists during the early phases of translational research with novel radionuclides for radionuclide therapy. An appropriate medical physics support group also requires the involvement of other supporting disciplines, such as service engineers, computer scientists, and medical imaging and laboratory technologists.

5.3.3 Guidance from professional organisations

The nuclear medicine and medical physics communities have already contributed a considerable number of publications to the field, such as standard operating procedures, guidelines and recommendations related to acceptance testing and routine quality control of nuclear medicine instrumentation, the use of internal dosimetry methods, and the education and training of medical physicists in nuclear medicine. During the last decade, two joint research projects (MetroMRT and MRTDosimetry), driven by the European Association of National Metrology Institutes (EURAMET), have focused on the advancement of medical physics and metrology techniques, and implementation of dosimetry for radionuclide therapy.

5.3.4 Equipment setup

The workflow for measurements and calculations in radionuclide therapy is very extensive. To begin with, the correct instrumentation and equipment, accepted by a medical physics expert, should be in place. From a metrology perspective, quantitative measurements should be traceable, and the use of proper physical quantities based on the latest knowledge that is available in the field. This means that all radionuclide calibrators or activity metres that are used in the production, supply, research, clinical or preclinical environment should be properly calibrated. Independently, whether these devices are used for diagnostic or therapeutic applications, it should be known how accurate and traceable the determined activity is. These devices are the basis for use in phantom measurements, or for the administration of activity in small animals, as well as in patients. It is known that measurements with radionuclide calibrators are more reliable and more accurate when the characteristics, composition, and geometry of the recipient, source volume, and possible use of copper filters are considered for the used radionuclide (48). It is also clear that the accurate determination of activity is very important in the overall picture of nuclear medicine applications. It usually has a direct impact on all further steps, such as system calibration, image quantification, dosimetry, and the derived dose-effect relationships.

Besides radionuclide calibrators, other medical radiological imaging equipment is involved. Before these devices are used in a preclinical or clinical environment, they should go through a thorough acceptance testing program, and their performance should be investigated and verified with respect to the nationally required, or internationally recommended acceptability criteria (49,50). The calibration, fine-tuning and settings of medical imaging equipment, such as SPECT/CT or PET/CT cameras, are extremely important for

their (pre)clinical use, but also for all related clinical research. The acquisition and reconstruction parameter settings can influence the image quality considerably. Therefore, clinical trials that want to use the acquired data for quantification or dosimetry in the approval phase of new radiopharmaceuticals, are preceded by an extensive performance or quality analysis program. Such an assessment might even lead to the adjustment of the used equipment settings for a particular aim of the clinical study or trial. For that purpose, medical physicists assess the system performance by means of quality control measures or image quality phantom measurements. These technical investigations of the involved equipment, which can be equipment specific and very detailed, can take a considerable amount of work and time, and is often not seen as an important part of the preparatory process. This work should of course not slow down the progress of research with the novel radionuclides. For that reason, it is very important that these investigations, and build-up of experience, should commence as early as possible in the translational pathway, and in parallel with the radiopharmaceutical development, to speed up the process.

5.3.5 Quantitative Imaging with novel radionuclides

There is a growing interest in quantitative imaging, which means that the obtained image data can be quantified in relation to the administered activity and the *in vivo* observed activity distribution. The quantitative information that is added to the image is of course very helpful for the application and improvement of pharmacokinetic analysis and internal radiation dosimetry workflow. The EANM strives for the harmonisation of quantitative imaging techniques by means of research initiatives, such as the EARL accreditation in PET/CT (51). These accreditation efforts for PET/CT imaging have been shown to be indispensable for the use of quantitative information in multi-centre clinical trials. Efforts are underway to extend the EARL approach to other applications in PET/CT, and to prepare for a similar approach in SPECT/CT. The latter is very important since many of the novel radionuclides allow for the use of SPECT/CT imaging.

Some radionuclides that recently found application in the field have complex decay schemes and commercial imaging solutions have been shown to be inadequate for qualitative and quantitative imaging. The different types of emitted radiation in these radionuclides brings considerable detection challenges and the requirement for advanced data correction techniques. Nevertheless, some recent and successful studies have shown that clinical imaging protocols and quantitative imaging can be achieved for some promising radionuclides, like Ra-223, Ac-225, and Th-227 (52,53). For that, advanced image correction and specific reconstruction techniques have been developed and evaluated with clinical examples. In the context of the MRTDosimetry project, the feasibility of equipment calibration, and acquisition protocol harmonisation for quantitative Lu-177 SPECT-CT was achieved and demonstrated in the field by means of (inter)national comparison exercises (54).

5.3.6 Image acquisition and processing

Image processing methods and data correction techniques might come with a high computational burden that can only be addressed with dedicated computational infrastructures that require specific implementation and support. Fortunately, fast graphics processing unit or GPU-based Monte-Carlo techniques have been shown to improve Lu-177 imaging (55). Recently, efforts have led to the establishment of clinical SPECT/CT protocols for Tb-161 as well (56). However, raw acquisition data that is exported for offline processing using research tools, can bring extra challenges that are the result of the medical device regulation (MDR; EU Regulation 2017/745 for medical devices). Software that is clinically used for medical imaging research, can be considered a medical device, and therefore should go through a rigorous safety and performance assessment and might require quality assurance, commissioning, clinical validation, risk analysis, and surveillance.

It is important for the field to standardise the way medical images are being acquired or exchanged in between imaging systems. Therefore, the Digital Imaging and Communications in Medicine (DICOM) standard, also known as ISO standard 12052:2017, is the establishment of several agreements between manufacturers, and it is very important in clinical practice. The unambiguous use of time references for

acquired or reconstructed data, is an example of harmonisation over system design and development in nuclear medicine. The use of clear time signatures is essential for nuclear medicine imaging data, since decay correction, is dependent upon this, and it is part of the image quantification process, and most certainly for short half-life radionuclides. The use of novel imaging techniques, such as quantitative SPECT/CT, will require further application and development of this DICOM standard.

5.3.7 New technology

Technological improvements have allowed for a miniaturisation of nuclear medicine imaging equipment. Dedicated SPECT, PET, and derived hybrid imaging modalities for small animals have revolutionised the domain of biomedical research and allow for rapid development of novel radiopharmaceuticals that can be analysed using small animals. Nowadays, dedicated preclinical facilities and small animal research laboratories have emerged and work in close cooperation with pharmaceutical research fields and industry. The dedicated preclinical instrumentation and research equipment is sometimes more open to customization or adjustment of specific device settings, compared to clinical devices. Good cooperation with the device manufacturer enhances insights and allows for a quicker response to technological challenges. In fact, just being able to adjust specific parameters or system settings can be an advantage in a rapidly evolving domain, like radiopharmaceutical research. It is also important to involve medical physics experts with these devices, so they can tailor equipment calibration and usage with the clinical counterparts.

Many clinical devices, on the other hand, are limited or not open to the adjustment of system parameters, and extraction of the acquired data in a raw supported format is not always possible, or even allowed. Information is usually proprietary which makes the use of these devices for clinical research difficult, especially when specific fine-tuning for the application of novel radionuclides is required. Good cooperation with the manufacturers will be necessary for future challenges in radionuclide therapy applications. There are some important manufacturing challenges to address, such as the compensation for high count-rate measurements during therapy, the influence of dead-time effects at the detector level, and the consistent use of nuclear data and physical quantities.

On the other hand, in conventional nuclear medicine, solid-state based detector technology, such as cadmium-zinc-telluride or CZT detectors, is revolutionising medical imaging equipment (57). Together with innovative detector configurations, we expect that these devices will solve some of the challenges that were mentioned above, such as high count-rate imaging during therapy (58). Some of these detectors also have better energy resolution, which might be favourable for the application of data correction techniques, such as scatter correction, and usefulness for image quantification.

5.3.8 Quality control

The calibration of nuclear medicine instrumentation also brings the need for periodic verification, which is the purpose of quality control. All systems that have been calibrated at a certain moment in time, can gradually or abruptly show signs of deviation or drift, and thus require verification of the calibration status at regular intervals. The frequency of the quality control tests depends on the type of device or the purpose of the application. A medical physicist should be involved to set up this continuous process of quality assurance.

Quality assurance procedures might require a higher level of sophistication with the introduction of new medical imaging equipment, radiation detection instrumentation, and the use of novel radionuclides. The assessment of radionuclide impurities might not only be necessary for pharmaceutical quality assurance of radiopharmaceutical products, but also to influence the calibration of imaging equipment and be of importance for internal radiation dosimetry calculations. A more systematic involvement of gamma ray spectrometry, that of course should be supported by a quality assurance framework as well, could be essential for the long-term assessment of the stability of the calibration of equipment, such as radionuclide calibrators, SPECT, and PET cameras.

5.3.9 Image processing and dosimetry

The next step in the dosimetry workflow is to apply image processing to the acquired imaging data. For that, standardisation of the different parts of the workflow might be very useful. First, it might be necessary to spatially align or register the images that were acquired at different time points, from different imaging modalities, for image fusion and comparison analysis, or to assess the uptake of activity in the same location over time. During processing, regions can be defined for which image segmentation or delineation of structures can be helpful. Nowadays, automated deformable image registration techniques exist, and dedicated image segmentation methods based on artificial intelligence are useful software tools for lesion or organ delineation in the context of radionuclide therapy planning (59). Advanced treatment planning systems make use of structure sets that define regions-of-interest, and which allow for the computation of quantifiable image intensities, such as activity concentration, or the volume and shape of delineated structures. Using the DICOM standard, these structures can be exchanged between different morphological and functional imaging data sets.

The committee on Medical Internal Radiation Dose (MIRD) of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) proposed a general scheme or formalism for the calculation of the absorbed dose from the observed activity in indicated regions. The source and target regions in the MIRD formalism can be defined at different levels, such as the cellular, voxel, (sub)organ, or even at the level of the whole body. Given the activity distribution derived from images, the absorbed dose can also be determined using local energy deposition methods, point-dose kernel convolution techniques, or by means of full Monte Carlo based radiation transport calculations (60). Software programs for radionuclide therapy planning have evolved from in-house developed research tools, to very advanced and CE marked solutions that are commercially available (61–63).

Non-imaging data, such as sampled activity concentrations at different time points in blood, urine, or faeces, can also be helpful for the purpose of internal dosimetry calculations. Usually, a gamma counter is used to measure the activity concentration in these samples. As mentioned before, gamma counters should be calibrated and verified, and they be included in the metrology framework supporting radionuclide therapy planning, so that results can be expressed in traceable quantities of activity. Gamma counters can help with the assessment of the long-term stability of equipment cross-calibrations (64). Gamma ray spectrometry might be an indispensable technique to support the translation of novel radionuclides for radionuclide therapy.

The EANM dosimetry committee provided a guidance document for good practice in clinical dosimetry reporting (65). Advanced data and image processing software will require commissioning and validation before use in the clinical environment. Moreover, all software and other tools that are used for calculation and reporting will require thorough assessment of traceability as mentioned in the context of the end-to-end metrology, and the uncertainty of the calculations should be analysed and reported with the results (66).

Currently, there is not a clear guideline on which radiation dosimetry approach is required for radionuclide therapies, whether for (pre)clinical trials, or for clinical application (67). An extensive dosimetry assessment that would include the acquisition of quantitative imaging over many time points, can require a lot of resources and equipment time. Together with the personnel cost, this time can be expensive in a busy clinical environment. For each nuclear medicine department, it might take quite some planning to merge the dosimetry workflow for radionuclide therapy with the other ongoing clinical work. Indeed, the healthcare infrastructure might pose a key challenge in the implementation of radionuclide therapy dosimetry (68). Increased equipment and the need for dedicated staffing are difficult to justify in the absence of assured reimbursement, which emphasises the need for dosimetry. Sufficient dosimetry data from preclinical and early clinical trials, and personalised treatment planning should be a necessary requirement for obtaining a marketing authorisation for new radiopharmaceuticals. The principle of optimization requires that toxicity is expressed in terms of activity and absorbed dose to target volumes and organs-at-risk. Some of the novel radionuclides, for example those that have a prevalent Auger cascade, have the potential to localise to the cell nucleus and bind to the DNA. This special case for low-LET radiation, but also the introduction of alpha

emitters, might need special attention and considerable effort in the translation pathway of these radiopharmaceuticals.

6. Conclusion

The involvement of metrology and medical physics is of crucial importance for the overall process of standardisation and harmonisation along the translational pathway of novel radiopharmaceuticals for therapy. Below, we list some relevant guidelines for the calibration and quality assurance of equipment, and the application of dosimetry.

6.1 Relevant Guidelines

6.1.1 Calibration and quality assurance of equipment

- Protocol for establishing and maintaining the calibration of medical radionuclide calibrators and their quality control. Measurement Good Practice Guide No. 93. Gadd R, Baker M, Nijran KS, Owens S, Thomas W, Woods MJ, et al. Teddington: National Physical Laboratory; 2006. https://www.npl.co.uk/gpgs/maintaining-the-calibration-medical-radionuclide
- Criteria for acceptability of medical radiological equipment used in diagnostic radiology, nuclear medicine and radiotherapy. European Commission, Directorate-General for Energy, (2013). Publications Office. https://data.europa.eu/doi/10.2768/22561
- AAPM Report No. 181 – The Selection, Use, Calibration, and Quality Assurance of Radionuclide Calibrators Used in Nuclear Medicine (2012)
- AAPM Report No. 126 – PET/CT Acceptance Testing and Quality Assurance (2019)
- AAPM Report No. 177 – Acceptance Testing and Annual Physics Survey Recommendations for Gamma Camera, SPECT, and SPECT/CT Systems (2019)
- Acceptance testing for nuclear medicine instrumentation. Busemann Sokole, E., Płachcínska, A., Britten, A. et al. Eur J Nucl Med Mol Imaging 37, 672–681 (2010). https://doi.org/10.1007/s00259-009-1348-x
- Routine quality control recommendations for nuclear medicine instrumentation. On behalf of the EANM Physics Committee:., Busemann Sokole, E., Płachcínska, A. et al. Eur J Nucl Med Mol Imaging 37, 662–671 (2010). https://doi.org/10.1007/s00259-009-1347-y
- EANM Technologist's Guide: Quality Control of Nuclear Medicine Instrumentation and Protocol Standardisation. Camoni, Luca & Rep, Sebastijan & Santos, Andrea & Attard, Marie. (2017).
- European Commission. Medical Device Regulation (MDR). Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. https://eur-lex.europa.eu/eli/reg/2017/745/2020-04-24

6.1.2 Dosimetry for radionuclide therapy

- Council of the European Union. European Council Directive 2013/59/Euratom on basic safety standards for protection against the dangers arising from exposure to ionising radiation and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom. Official Journal of the EU. 2014;L13:1–73. https://eur-lex.europa.eu/eli/dir/2013/59/oj
- ICRU REPORT 96, Dosimetry-Guided Radiopharmaceutical Therapy. Journal of the ICRU, Sgouros, G., Bolch, W. E., Chiti, A., Dewaraja, Y. K., Emfietzoglou, D., Hobbs, R. F., Konijnenberg, M., Sjögreen-Gleisner, K., Strigari, L., Yen, T.-C., & Howell, R. W. (2021). 21(1), 1–212. https://doi.org/10.1177/14736691211060117
- EANM Technologist's Guide: Radionuclide Metabolic Therapy. Hogg, Peter & Veloso, Vanessa & Pește an, Claudiu. (2013).

- EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting. Lassmann, M., Chiesa, C., Flux, G. et al. Eur J Nucl Med Mol Imaging 38, 192–200 (2011). https://doi.org/10.1007/s00259-010-1549-3
- EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry. Hindorf, C., Glatting, G., Chiesa, C. et al. Eur J Nucl Med Mol Imaging 37, 1238–1250 (2010). https://doi.org/10.1007/s00259-010-1422-4
- EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations. Gear, J.I., Cox, M.G., Gustafsson, J. et al. Eur J Nucl Med Mol Imaging 45, 2456–2474 (2018). https://doi.org/10.1007/s00259-018-4136-7
- Bolch WE, Eckerman KF, Sgouros G, Thomas SR. MIRD pamphlet No. 21: a generalized schema for radiopharmaceutical dosimetry--standardization of nomenclature. J Nucl Med. 2009 Mar;50(3):477-84. doi: 10.2967/jnumed.108.056036. PMID: 19258258.
- Sgouros, G., Roeske, J. C., McDevitt, M. R., Palm, S., Allen, B. J., Fisher, D. R., Brill, A. B., Song, H., Howell, R. W., Akabani, G., SNM MIRD Committee, Bolch, W. E., Brill, A. B., Fisher, D. R., Howell, R. W., Meredith, R. F., Sgouros, G., Wessels, B. W., & Zanzonico, P. B. (2010). MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 51(2), 311–328. https://doi.org/10.2967/jnumed.108.058651
- Dewaraja, Y. K., Frey, E. C., Sgouros, G., Brill, A. B., Roberson, P., Zanzonico, P. B., & Ljungberg, M. (2012). MIRD pamphlet No. 23: quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 53(8), 1310–1325. https://doi.org/10.2967/jnumed.111.100123

7. Non-clinical safety & pharmacology

7.1 General remarks

7.1.1 Radiopharmaceuticals and non-clinical studies

In order to proceed from preclinical development to clinical application, besides the need to define and ensure the chemical and pharmaceutical quality of a new radiopharmaceutical in the context of PRISMAP`s novel radionuclides, it is essential to establish data to predict its behaviour in the human body by appropriate preclinical tests. Such “non-clinical studies” include investigations on pharmacology and toxicology and should establish a safety and efficacy profile of a new radiopharmaceutical. The type of data expected for radiopharmaceuticals are outlined in Figure 5.

In European Directive 2001/83/EC, the annex I appreciates that toxicity of a radiopharmaceutical may be associated to its radiation dose. In diagnosis, this is a side effect of the use of radiopharmaceuticals; in therapy, it is the intended property. The evaluation of safety and efficacy of radiopharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally accepted system by a particular route of administration.

Non-clinical studies not only show the safety profile in animals, but also provide important information about the fate of radiopharmaceuticals in the body (**A**bsorption, **D**istribution, **M**etabolism, **E**xcretion, ADME, whereby absorption typically plays a minor role for radiopharmaceuticals). Additional investigations such as in vitro affinity studies, dynamic biodistribution in appropriate animal models additionally are included. All of this information is used to decide if the candidate radiopharmaceutical can proceed into the first human (clinical) study and, if so, what doses to use.

The importance of **non-clinical data** for assessment of clinical safety changes across the different phases of drug development. It **is highly important for the preparation of First-in-Human (FIH)** studies and their

importance decreases until marketing authorization except for carcinogenicity, mutagenicity and developmental and reproductive toxicity. In this regard, radiopharmaceuticals are different. Due to unavoidable and wanted radioactive properties, the added value of mutagenicity studies and long-term carcinogenicity studies is not always given. Other European Directives, applying to radiopharmaceuticals may also apply to non-clinical studies, related to radiation safety and Good Laboratory Practices.

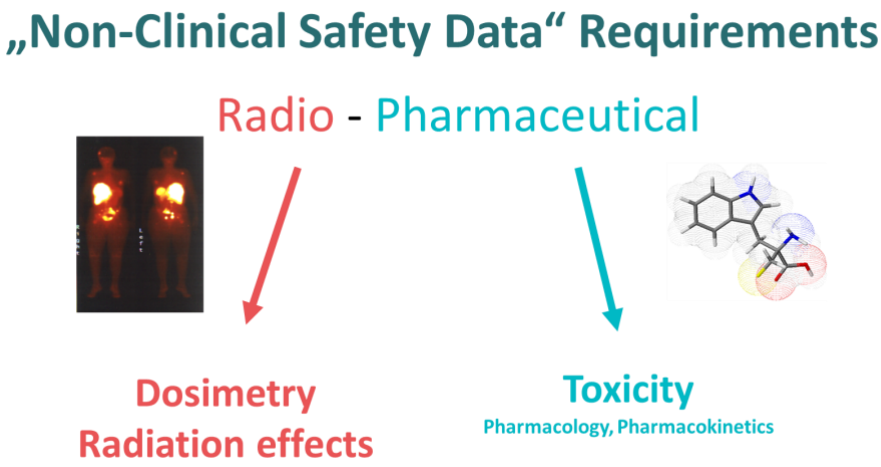

Figure 5. Non-clinical Safety data of radiopharmaceuticals is comprised on the one hand of data related to the effects of radiation including dosimetry, and on the other hand requires data on the toxicity effects of the non-radioactive molecule, including pharmacology and pharmacokinetics

A recent publication (70) specifically addresses the aspects of non-clinical testing of radiopharmaceuticals and gives practical considerations and detailed guidance on how to navigate the regulatory landscape. In the following the major regulatory documents are listed with major aspect in relation to PRISMAP`s activities.

7.1.2 Sources of guidance documents for non-clinical requirements of pharmaceutical compounds

Generally, there are three main sources of guidance for non-clinical requirements for safety and pharmacology, namely, the EMA scientific guidelines, reflection papers etc, the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines and the OECD (Organisation for Economic Co-operation and Development) protocols, the latter of importance for definition of Good Laboratory Practices (GLP) guidelines. The details of the European Public Assessment Reports provided by the EMA Website for every centralised authorised product may also be helpful. It should be noted that a dedicated guideline describes the information to be included in the summary of product characteristics (SmPC) and package leaflet (PL) for radiopharmaceuticals.

The general non-clinical requirements for pharmaceuticals are given in the ICH M3 (R2) note for guidance for all medicinal products e.g. regarding the timing requirements in the three different stages: before First-in-Human studies, during clinical development and on marketing authorisation. In the same guideline, they provide directions on the type and duration of non-clinical safety studies, their timing to support the conduct of clinical trials and marketing authorisation for pharmaceuticals. For radiopharmaceuticals, this guidance offers five different approaches for exploratory clinical trials: two different microdose approaches, single-dose trials at sub therapeutic doses or into the anticipated therapeutic range and two approaches for multiple dose trials. Although radiopharmaceuticals are covered by the EMEA/CHMP/QWP/306970/2007 Guideline on Radiopharmaceuticals, no EMA guidance was available to specifically support non-clinical development of this type of medicinal product.

Some indications on the recommended scope of the non-clinical testing specific to radiopharmaceuticals can be found in the FDA guideline documents related to late radiation toxicity, exploratory IND studies, Microdose Radiopharmaceutical Diagnostic Drugs, Oncology Therapeutic Radiopharmaceuticals, Codevelopment of Two or More New Investigational Drugs and Designing and Conducting Toxicity Studies.

7.1.3 Preparation of a guideline for non-clinical requirements for radiopharmaceuticals

The history of work on guideline for non-clinical requirements for radiopharmaceuticals started in Vienna in April 2014 (PAM) with the presentation on "Preclinical safety data for Radiopharmaceuticals" by C. Decristoforo in line with the EANM Position paper on requirements for toxicological studies in the specific case of radiopharmaceuticals (69). In June 2015 the work of the Safety Working Party (SWP) Drafting group (DG) of EMA started, which generated a "Concept paper on the development of guidance on the non/clinical evaluation of radiopharmaceuticals", followed by a public consultation phase July 2017- October 2017. On March 2018 the drafting of the guideline was started and published on 22/11/2018, with consultation dates 22/11/2018 to 30/06/2019; EMA/CHMP/SWP686140/2018). The business continuity plan had to consider Brexit, the EMA relocation and COVID-19 and thus, this activity was suspended temporarily, hence the guideline has not been adopted.

There were certain prerequisites taken into consideration in the development of such a specific guideline for non-clinical requirements for radiopharmaceuticals. It needed to address a broad range of indications, half-life from minutes to days, a broad range in molecular weight, radiodiagnostic and radiotherapeutic use as well as radionuclide alone or linked to non-radioactive components. It needed to be in line with the general guidance for timing and duration of non-clinical safety studies from ICH M3(R2) and the Directive 2010/63/EU on the protection of animals used for scientific purposes. The guideline should provide guidance on the required non-clinical data to support clinical development and approval of radiopharmaceuticals. It should also complement currently available guidelines (such as ICH M3(R2), ICH S6(R1), ICH S9) or the EMA guideline on "strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products" and only "ready to use" radiopharmaceuticals were addressed. The new guideline is focused on opportunities to targeted non-clinical programs for the non-radioactive part according to specific development settings and product types and was not intended to duplicate guidance related to dosimetry.

7.1.4 Relevance to the PRISMAP Project

From the perspective of PRISMAP applying novel radionuclides including novel production modes one of the main aims of non-clinical testing is to provide supportive data to determine the activities of the radionuclide in question to use in a clinical trial. This decision will be driven not only by the physical characteristics of the radionuclide but also by the molar activity of the radionuclide and the impurity profile resulting from the selected production mode - which will determine the radiolabelling yields and radiochemical purity as well as the molar activity of the radiolabelled molecule. For example, in therapeutic applications the activities of a novel radionuclide required may result in masses of a targeting peptides (derivatives of regulatory peptides) that may exert pharmacodynamic effects resulting in (severe) adverse effects and/or competitive occupancy of the target.

In the radiopharmaceutical development phase, it is important that comparative evaluation of molecules radiolabelled with various radionuclides is performed using standardised radiolabelling protocols and the effect of mass of tested compounds is used for in vitro and in vivo studies. In this chapter we give an overview of the current guidance documents to assess dosimetry, toxicity, pharmacology of radiopharmaceuticals, which are developed with the aim to be used in clinical trials (71).

7.2 Non-clinical safety studies

7.2.1 Radiation Ddosimetry as part of non-clinical safety

Radiation dosimetry aspect are covered by Guidance on medical exposures in medical and biomedical research, and further in EURATOM Directives. Any radiopharmaceutical with a new radionuclide is a new radiopharmaceutical from the regulatory perspective. In the application for a First-In-Human study, animal studies are required to estimate the effective dose and organ doses in humans. Two major guidance documents for dosimetry analysis are listed below.

7.2.2 Dosimetry Swiss perspective: "Guidance document Authorisation radiopharmaceutical HMV4"

This guidance document states:

Internal dosimetry is the estimation of absorbed radiation by the organs and the total body deposited by the incorporated radionuclide in the body. Pharmacokinetic information should be sufficient for calculating the dosimetry of radiodiagnostic agents. Data from animal studies (extrapolated to estimated doses in humans) should be confirmed as relevant or superseded by data measured in humans. The effects of age, clinical condition and, importantly, impairment of hepatic or renal function should be factored into dose estimations.

Reference to the Medical Internal Radiation Dosimetry (MIRD) schedule is recommended when calculating the absorbed doses. *The model used to calculate cumulative activity (time integral of the activity) in the source organs should be explained, and the data source (animal experiments or studies in humans) stated. Physical parameters, e.g. absorbed dose in the target organ per unit of cumulative activity in the target organ should be taken from the MIRD tables.*

The weighting factors established by the International Commission on Radiological Protection (ICRP) should be used when calculating the effective doses. *Since these factors do not apply to children, pregnant women or the elderly, appropriate adjustments should be made for these patient groups.*

If other methods are used to calculate the doses absorbed by organs, corresponding details should be provided and enclosed with the original reports.

The dose absorbed by the organ receiving the highest exposure and by all other organs relevant to the calculation of the effective dose-equivalent should be stated (units: mGy/MBq, mGy per unit of activity). ***The estimation of the radiation dose must be summarised in terms of the effective dose-equivalent in relation to the ICRP weighting factors, stated in Sv/MBq.***

7.2.3 Guidance for Preclinical Studies with Radiopharmaceuticals by International Atomic Energy Agency, Vienna (Austria)

This new IAEA document provides detailed guidance on the conduct of preclinical dosimetry testing. For brevity, we only list below the topics addressed, for the whole text we refer the reader to the link of this IAEA guidance.

- Study design
- MIRD principle for dosimetry calculations
- Pharmacokinetic modelling of *in vivo* data to derive TAC
- Biodistribution data organ concentrations
- Quantitative data of small animal SPECT / PET imaging
- Dosimetry phantoms for organ absorbed dose - S-values in small animals -
- MOBY/ ROBY phantom dosimetry models
- Voxel based dosimetry models

- Small scale dosimetry models
- Extrapolation of animal dosimetry to human dosimetry

7.2.4 Toxicity

As stated above safety aspects related to the radionuclide are covered by dosimetry. The relevant guidelines on the toxicity referring only to the non-radioactive component of radiopharmaceuticals are listed below.

7.2.5 Guideline on the non-clinical requirements for radiopharmaceuticals (not adopted yet) (EMEA/CHMP/SWP/686140/2018)

This draft guideline by EMA allows a risk based, targeted approach for radiopharmaceuticals. For different scenarios as outlined below, where evidence needs to be only partly generated, a targeted (in the sense of a reduced) non-clinical programme for the non-radioactive part of the radiopharmaceutical can be considered:

a) Radionuclide changed in a known radiopharmaceutical

b) Radionuclide added to a known non-radioactive pharmaceutical

c) Minimal change of the non-radioactive part of a radiopharmaceutical

For these scenarios the guidance states that *the main focus should be laid on the evaluation of the target organs of biodistribution and possible persistence of the modified non-radioactive part possibly leading to so far unknown toxic effects even if the change is claimed to be minimal. A biodistribution study in one species with single application and integrated measurement of toxicity endpoints can be generally considered sufficient. If off target binding is likely to be minimal from the results of the dosimetry study, histopathological examination may be limited to target organs.*

*In the case of an **exploratory trial** with intended clinical dose of the radiopharmaceutical being a microdose according to approach 1 or approach 2 as outlined in ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals **(see** Table 7 **in Appendix II)** and if, in addition, the absence of pharmacological activity of the non-radioactive part could be demonstrated, such a biodistribution study could be waived.*

The recommendations for a non-clinical safety programme of a new radiopharmaceutical using microdose are described as follows:

The majority of clinical trials performed with radiopharmaceuticals falls under the scope of exploratory trials. Therefore, the microdose approach as outlined in ICH M3(R2) can be applied. According to the definition given there, a microdose is a total dose ≤ 100 µg (no inter-dose interval limitations) and total dose ≤ 1/100th NOAEL and ≤1/100th pharmacologically active dose (approach 1), or a total cumulative dose ≤ 500 µg, maximum of 5 administrations with a washout between doses (6 or more actual or predicted half-lives) and each dose ≤ 100 µg and each dose ≤ 1/100th of the NOAEL and ≤ 1/100th of the pharmacologically active dose (approach 2). Due to differences in molecular weights between biologicals and chemicals, and due to the fact that pharmacological and toxicological effects are usually driven by the molar amount and not by the mass, a maximum dose above 100 µg based on molar amount can be accepted for high molecular weight molecules taking into account the potency of the molecule (approach 1 for biologicals). Approach 2 may be less relevant for biologicals with a long elimination half-life. Accordingly, the minimal requirements for the non-clinical development of a radiopharmaceutical carrying a new non-radioactive part using the microdose approach are outlined below. This non-clinical package is usually also considered sufficient for marketing authorisation applications using the same dosing regimen.

Recommendations for diagnostic radiopharmaceuticals:

In most cases microdose approach 1 of ICH M3(R2) will be used for radiodiagnostics since no pharmacological effect is intended and only a very small mass dose is administered after single administration.

7.2.6 Guidance for Preclinical Studies with Radiopharmaceuticals by the International Atomic Energy Agency, Vienna (Austria)

As in the previous chapter for the sake of brevity, only the topics related to toxicology covered in this IAEA-guidance are mentioned below:

- Rationale and general principles
- Existing guidelines and recommendations
- Guidance on therapeutic radiopharmaceuticals
- Calculation of human equivalent dose

7.2.7 Pharmacology

General guidance on safety pharmacology studies of pharmaceuticals can be found in ICH S7A. Specific guidance for pharmacology assessment of radiopharmaceuticals can be found in the documents detailed below.

7.2.8 Guideline on the non-clinical requirements for radiopharmaceuticals (not adopted yet) (EMEA/CHMP/SWP/686140/2018)

Again, for the scenario of a known or minimally changed non- radioactive part of a new radiopharmaceutical the following recommendations related to non-clinical pharmacology testing are given.

In case no reference is possible to previous applications or other public data using the identical non-radioactive part of the investigational radiopharmaceutical, the reduced non-clinical programme outlined below for a known or minimally changed non-radioactive part should be considered.

Pharmacology

The appropriate characterisation of pharmacology of the non-radioactive part alone is also expected in the case where the non-radioactive part of an already known radiopharmaceutical is claimed to be minimally changed. Emphasis should be on in vitro target/ receptor profiling. The selectivity and specificity of the non-radioactive part as well as secondary pharmacodynamics, defined as effects on other than the desired therapeutic targets, should be critically evaluated and documented. Measurable pharmacodynamic effects are normally not expected to be seen from the non-radioactive part of most radiopharmaceuticals for diagnostic or therapeutic purposes. However, evidence for the absence of pharmacodynamic effects is expected, and should be supported by appropriate data. If no data are provided, the applicant must justify the absence of in vitro/in vivo pharmacology data even in the case of a minimal change to the molecule.

Pharmacokinetics

For such minimally changed radiopharmaceuticals information on in vivo stability should be available. In addition, the biodistribution study performed in healthy animals of a relevant species including dosimetry should be thoroughly evaluated to detect any change in biodistribution and target organs related to the non-radioactive part compared to the former, known molecule. For radiotherapeutics, the study may be performed in an animal model of disease, if appropriate, to support that the targeted area organ will still be reached adequately.

For new diagnostic radiopharmaceuticals the following recommendations are given:

Pharmacology

Radiodiagnostic agents are not intended to exert pharmacological activity, but evidence for the absence of pharmacological activity of the non-radioactive part should be provided. In this context, in vitro target/ receptor profiling is usually sufficient.

Pharmacokinetics

A biodistribution study including dosimetry should be performed with a single dose of the radiodiagnostic. Information on in vivo stability, distribution and elimination should be available to allow estimation of tissue and whole-body radiation doses in the clinic and to identify target organs for distribution and persistence of the radiodiagnostic. If relevant, information should be provided on absorption and biotransformation

7.2.9 Guidance for Preclinical Studies with Radiopharmaceuticals, International Atomic Energy Agency, Vienna (Austria)

Primary pharmacology evaluation, either in the form of animal testing or in vitro testing, should be conducted to adequately elucidate the molecular mechanism of action. Additionally, a separate safety pharmacology (i.e. the agent's effects on vital organs and signs) evaluation is not necessary since these parameters are normally evaluated either during the ligand induced toxicology study or the biodistribution study or both.

More details on this topic can also be found in (70).

7.3 Relevant Guidelines - non-clinical safety & pharmacology

- Directive 2001/83/EC, "Community code relating to medicinal products for human use" as amended, in particular Directive 2001/83/EC Art 10(4) and Part II of the 100 Annex I of Directive 2001/83/EC, as amended. 101
- Directive 2013/59/Euratom 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, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom.
- Directive 2004/10/EC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances. European Commission, Directorate-General for Environment NS and Civil Protection. Guidance on medical exposures in medical and biomedical research. Luxembourg: OOPEC; 1999
- EMA/CHMP/167834/2011 - Core summary of product characteristics (SmPC) and package leaflet for radiopharmaceuticals
- ICH M3 (R2) Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals, CPMP/ICH/286/95, European Medicines Agency, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002941.pdf.
- EMEA/CHMP/QWP/306970/2007 Guideline on Radiopharmaceuticals https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-radiopharmaceuticals-revision-1_en.pdf
- FDA guidance 2011: Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals. https://www.fda.gov/files/drugs/published/Nonclinical-Evaluation-of-Late-Radiation-Toxicity-of-Therapeutic-Radiopharmaceuticals.pdf
- FDA/ICH Guidance Document: "Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies" https://www.fda.gov/files/Guidance-to-Industry-and-Reviewers---Exploratory-IND-Studies-%28PDF%29.pdf
- FDA Guidance Document: Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations, Guidance for Industry. https://www.fda.gov/media/107641/download
- FDA/ICH Guidance Document: Oncology Therapeutic Radiopharmaceuticals: Non-Clinical Studies and Labeling Recommendations, Guidance for Industry. https://www.fda.gov/media/129547/download
- FDA/ICH Guidance Document: "Guidance For Industry, Codevelopment of Two or More New Investigational Drugs for Use in Combination" https://www.fda.gov/media/80100/download

- FDA/ICH Guidance Document: “Redbook 2000:IV.B.1 General Guidelines for Designing and Conducting Toxicity Studies” https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivb1-general-guidelines-designing-and-conducting-toxicity-studies
- EMA/CHMP/SWP/686140/2018: Guidance on nonclinical requirements for radiopharmaceuticals – draft https://www.ema.europa.eu/en/non-clinical-requirements-radiopharmaceuticals (accessed 11.03.2022)
- Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF
- ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals [Internet]. European Medicines Agency. 2018 [accessed 11.03.2022]. https://www.ema.europa.eu/en/ich-s6-r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals
- ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals, CHMP/ICH/646107/08, European Medicines Agency, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500043471.pdf.
- EMEA/CHMP/SWP/28367/07 (July 2017): "Guideline on strategies to identify and mitigate risks for first in 106 human and early clinical trials with investigational medicinal products" https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf
- EMA/CHMP/QWP/834816/2015 “Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials” https://www.ema.europa.eu/en/requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational-medicinal
- European Commission, Directorate-General for Environment, *Guidance on medical exposures in medical and biomedical research*, Publications Office, 1999, https://op.europa.eu/en/publication-detail/-/publication/0be8f9c1-e923-4817-845f-29d0dc87183d
- Guidance document Authorisation radiopharmaceutical HMV4 (Swiss authorities) https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/zl_hmv_iv/zl000_00_034d_wlzulassungvonradiopharmazeutika.pdf.download.pdf/ZL000_00_034e_WL%20Guidance%20document%20Authorisation%20radiopharmaceutical.pdf
- International Atomic Energy Agency, Vienna (Austria) (2021). Guidance for Preclinical Studies with Radiopharmaceuticals (IAEA-PC--8628). International Atomic Energy Agency (IAEA) https://inis.iaea.org/collection/NCLCollectionStore/_Public/52/073/52073217.pdf?r=1
- ICH S7A (June 2001): “Note for guidance on safety pharmacology studies for human 114 pharmaceuticals https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s-7-safety-pharmacology-studies-human-pharmaceuticals-step-5_en.pdf
- OECD-Good Laboratory Practices (GLP) guidelines

Conclusions

The lack of specific rules and guidelines applicable for the clinical translation of novel radionuclides provides considerable room for interpretation by pharmaceutical regulatory authorities and the research community. This deliverable provides an in-depth analysis of the current landscape for the European radiopharmaceutical legal regulatory framework. To provide standardisation and harmonisation within PRISMAP it gives guidance and recommendations for the production and radiopharmaceutical research and development process in the application of novel radionuclides. The initial topics deal with quality data required for the translation process. It was considered important to provide definitions of terms and nomenclature for the specifications of PRISMAP radionuclides, and then touches more specifically on the production process when considering GMP, keeping in mind the expectations of authorities in how the data should be presented. Quality control and specifications are addressed separately with references to Ph.Eur., recent guidelines and

recommendations from professional organisations. The involvement of metrology and medical physics is of utmost importance in defining calibration standards for novel radionuclides. These data are needed to support pre-clinical studies for the translational radiopharmaceutical development process. The final part provides major documents and their relation to PRISMAP in the context of safety; involving “non-clinical study” requirements, including important recommendations from EMA and IAEA, to create a harmonised approach within PRISMAP.

This document provides guidance by defining general standards to meet regulatory requirements in the clinical translation process. In the further course of PRISMAP these data must be complemented by quality data for specific radionuclides, similar to monographs, based on the harmonised view provided in this document. Additionally, safety data of novel radionuclides and their radiopharmaceuticals as well as standards in relation to metrology and clinical equipment will be collected. These data will form a solid basis to support both radionuclide producers and the translational research within and outside PRISMAP, while providing a guide for pharmaceutical authorities in their evaluation process.

References

1. Decristoforo C, Penuelas I, Patt M, Todde S. European regulations for the introduction of novel radiopharmaceuticals in the clinical setting. Q J Nucl Med Mol Imaging. June 2017;61(2):135–44.
2. Hendrikse H, Kiss O, Kunikowska J, Wadsak W, Decristoforo C, Patt M. EANM position on the in-house preparation of radiopharmaceuticals. Eur J Nucl Med Mol Imaging. 20. January 2022;s00259-022-05694-z.
3. Schwarz SW, Decristoforo C, Goodbody AE, Singhal N, Saliba S, Ruddock P, et al. Harmonization of United States, European Union and Canadian First-in-Human Regulatory Requirements for Radiopharmaceuticals-Is This Possible? J Nucl Med. 27. September 2018;
4. Schwarz SW, Decristoforo C. US and EU radiopharmaceutical diagnostic and therapeutic nonclinical study requirements for clinical trials authorizations and marketing authorizations. EJNMMI Radiopharm Chem. 22. Mai 2019;4(1):10.
5. Peñuelas I, Vugts DJ, Decristoforo C, Elsinga PH. The new Regulation on clinical trials in relation to radiopharmaceuticals: when and how will it be implemented? EJNMMI Radiopharm Chem. 11. January 2019;4(1):2.
6. Bormans G, Buck A, Chiti A, Cooper M, Croasdale J, Desruet M, et al. Position statement on radiopharmaceutical production for clinical trials. EJNMMI Radiopharm Chem. 2017;2(1):12.
7. Hendrikse H, Kiss O, Kunikowska J, Wadsak W, Decristoforo C, Patt M. EANM position on the in-house preparation of radiopharmaceuticals. Eur J Nucl Med Mol Imaging. 20. January 2022;
8. Decristoforo C, Patt M. Are we „preparing“ radiopharmaceuticals? EJNMMI Radiopharm Chem. 2017;1(1):12.
9. Gillings N, Hjelstuen O, Ballinger J, Behe M, Decristoforo C, Elsinga P, et al. Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals. EJNMMI radiopharm chem. December 2021;6(1):8.
10. 5.19. Extemporaneous preparation of radiopharmaceuticals. In: European Pharmacopoeia. 10.0. European Directorate for the Quality of Medicines & HealthCare (EDQM); S. 807–12.
11. Lange R, ter Heine R, Decristoforo C, Peñuelas I, Elsinga PH, van der Westerlaken MML, et al. Untangling the web of European regulations for the preparation of unlicensed radiopharmaceuticals: a concise overview and practical guidance for a risk-based approach. Nucl Med Commun. May 2015;36(5):414–22.

12. Kolenc Peitl P, Rangger C, Garnuszek P, Mikolajczak R, Hubalewska-Dydejczyk A, Maina T, et al. Clinical translation of theranostic radiopharmaceuticals: Current regulatory status and recent examples. J Labelled Comp Radiopharm. August 2019;62(10):673–83.

13. Neels O, Patt M, Decristoforo C. Radionuclides: medicinal products or rather starting materials? EJNMMI Radiopharm Chem. 20. August 2019;4(1):22.

14. Decristoforo C, Neels O, Patt M. Emerging Radionuclides in a Regulatory Framework for Medicinal Products – How Do They Fit? Front Med. 28. May 2021;8:678452.

15. DAUE R. EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines [Internet]. Public Health - European Commission. 2017 [zitiert 7. January 2022]. Available under: https://ec.europa.eu/health/documents/eudralex/vol-4_en

16. Hooijman EL, Chalashkan Y, Ling SW, Kahyargil FF, Segbers M, Bruchertseifer F, et al. Development of [225Ac]Ac-PSMA-I&T for Targeted Alpha Therapy According to GMP Guidelines for Treatment of mCRPC. Pharmaceutics. 13. May 2021;13(5):715.

17. Pijarowska-Kruszyna JP-K, Garnuszek P, Decristoforo C, Mikolajczak R. Radiopharmaceutical Precursors for Theranostics. In: Theranostics - An Old Concept in New Clothing [Internet]. Intech Open; 2021. Available under: https://www.intechopen.com/chapters/74628

18. Todde S, Peitl PK, Elsinga P, Koziorowski J, Ferrari V, Ocak EM, et al. Guidance on validation and qualification of processes and operations involving radiopharmaceuticals. EJNMMI Radiopharm Chem. 2017;2(1):8.

19. Aerts J, Ballinger JR, Behe M, Decristoforo C, Elsinga PH, Faivre-Chauvet A, et al. Guidance on current good radiopharmacy practice for the small-scale preparation of radiopharmaceuticals using automated modules: a European perspective. J Labelled Comp Radiopharm. August 2014;57(10):615–20.

20. Boschi S, Lodi F, Malizia C, Cicoria G, Marengo M. Automation synthesis modules review. Appl Radiat Isot. June 2013;76:38–45.

21. Pretze M, Kunkel F, Runge R, Freudenberg R, Braune A, Hartmann H, et al. Ac-EAZY! Towards GMP-Compliant Module Syntheses of 225Ac-Labeled Peptides for Clinical Application. Pharmaceuticals (Basel). 6. July 2021;14(7):652.

22. International Atomic Energy Agency. Quality control in the production of radiopharmaceuticals. [Internet]. 2018 [accessed 23. March 2022]. Available under: https://www.iaea.org/publications/13422/quality-control-in-the-production-of-radiopharmaceuticals

23. Gillings N, Todde S, Behe M, Decristoforo C, Elsinga P, Ferrari V, et al. EANM guideline on the validation of analytical methods for radiopharmaceuticals. EJNMMI Radiopharm Chem. 12. February 2020;5(1):7.

24. Migliari S, Sammartano A, Boss M, Gotthardt M, Scarlattei M, Baldari G, et al. Development and Validation of an Analytical HPLC Method to Assess Chemical and Radiochemical Purity of [68Ga]Ga-NODAGA-Exendin-4 Produced by a Fully Automated Method. Molecules. 15. January 2022;27(2):543.

25. Radzik M, Pijarowska-Kruszyna J, Jaroń A, Maurin M, Decristoforo C, Mikołajczak R, et al. Development and validation of the HPLC method for quality control of radiolabelled DOTA-TATE and DOTA-TOC preparations. Nucl Med Biol. 3. December 2020;93:63–73.

26. van Andel L, Aalbersberg EA, Geluk-Jonker MM, Stokkel MPM, Beijnen JH, Hendrikx JJMA. The development and validation of a high performance liquid chromatography method to determine the radiochemical purity of [177Lu]Lu-HA-DOTA-TATE in pharmaceutical preparations. J Chromatogr B Analyt Technol Biomed Life Sci. 1. May 2021;1171:122605.

27. Di Iorio V, Boschi S, Sarnelli A, Cuni C, Bianchini D, Monti M, et al. [18F]F-PSMA-1007 Radiolabelling without an On-Site Cyclotron: A Quality Issue. Pharmaceuticals (Basel). 22. June 2021;14(7):599.

28. Migliari S, Sammartano A, Scarlattei M, Baldari G, Silva C, Ruffini L. A Rapid and Specific HPLC Method to Determine Chemical and Radiochemical Purity of [68Ga]Ga-DOTA-Pentixafor (PET) Tracer: Development and Validation. Curr Radiopharm. 2021;14(2):121–30.

29. Migliari S, Sammartano A, Scarlattei M, Serreli G, Ghetti C, Cidda C, et al. Development and Validation of a High-Pressure Liquid Chromatography Method for the Determination of Chemical Purity and Radiochemical Purity of a [68Ga]-Labeled Glu-Urea-Lys(Ahx)-HBED-CC (Positron Emission Tomography) Tracer. ACS Omega. 31. October 2017;2(10):7120–6.

30. Mora-Ramirez E, Santoro L, Cassol E, Ocampo-Ramos JC, Clayton N, Kayal G, et al. Comparison of commercial dosimetric software platforms in patients treated with 177 Lu-DOTATATE for peptide receptor radionuclide therapy. Med Phys. September 2020;47(9):4602–15.

31. European Commission. SAMIRA: Strategic Agenda for Medical Ionising Radiation Applications [Internet]. Brussels; 2021 Feb [accessed 21. March 2022] S. 25. Report No.: SWD(2021) 14 final. Available under: https://energy.ec.europa.eu/system/files/2021-02/swd_strategic_agenda_for_medical_ionising_radiation_applications_samira_0.pdf

32. Weber WA, Czernin J, Anderson CJ, Badawi RD, Barthel H, Bengel F, et al. The Future of Nuclear Medicine, Molecular Imaging, and Theranostics. J Nucl Med. December 2020;61(Suppl 2):263S-272S.

33. Yonekura Y, Mattsson S, Flux G, Bolch WE, Dauer LT, Fisher DR, et al. ICRP Publication 140: Radiological Protection in Therapy with Radiopharmaceuticals. Ann ICRP. September 2019;48(1):5–95.

34. Walrand S, Bakhtina K. Direct effect of the Directive Euratom 2013/59 on European hospitals hosting radionuclide therapies. Phys Med. 9. March 2022;96:121–2.

35. Sjögreen Gleisner K, Spezi E, Solny P, Gabina PM, Cicone F, Stokke C, et al. Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey. EJNMMI Phys. 4. December 2017;4(1):28.

36. European Commission. Directorate General for Energy. Developments in nuclear medicine: new radioisotopes in use and associated challenges : EU Scientific Seminar November 2019. [Internet]. LU: Publications Office; 2020 [zitiert 19. February 2021]. Verfügbar unter: https://data.europa.eu/doi/10.2833/905722

37. Konijnenberg M, Herrmann K, Kobe C, Verburg F, Hindorf C, Hustinx R, et al. EANM position paper on article 56 of the Council Directive 2013/59/Euratom (basic safety standards) for nuclear medicine therapy. Eur J Nucl Med Mol Imaging. January 2021;48(1):67–72.

38. Sgouros G, Bolch WE, Chiti A, Dewaraja YK, Emfietzoglou D, Hobbs RF, et al. ICRU REPORT 96, Dosimetry-Guided Radiopharmaceutical Therapy. J. ICRU. December 2021;21(1):1–212.

39. Zimmerman BE, Bergeron DE, Cessna JT, Fitzgerald R, Pibida L. Revision of the NIST Standard for (223)Ra: New Measurements and Review of 2008 Data. J Res Natl Inst Stand Technol. 2015;120:37–57.

40. Bergeron DE, Cessna JT, Coursey BM, Fitzgerald R, Zimmerman BE. A Review of NIST Primary Activity Standards for (18)F: 1982 to 2013. J Res Natl Inst Stand Technol. 2014;119:371–96.

41. Graves SA, Martin M, Tiwari A, Merrick MJ, Sunderland JJ. SIR-Spheres activity measurements reveal systematic miscalibration. J Nucl Med. 6. January 2022;jnumed.121.262650.

42. Cessna JT, Golas DB. The NIST radioactivity measurement assurance program for the radiopharmaceutical industry. Appl Radiat Isot. September 2012;70(9):2227–31.

43. Bergeron DE, Kossert K, Collins SM, Fenwick AJ. Realization and dissemination of activity standards for medically important alpha-emitting radionuclides. Appl Radiat Isot. 25. February 2022;184:110161.

44. Gadd R, Baker M, Nijran K, Owens S, Thomas W, Woods M, et al. Protocol for establishing and maintaining the calibration of medical radionuclide calibrators and their quality control. 2006;

45. Bergeron DE, Cessna JT. An update on 'dose calibrator 'settings for nuclides used in nuclear medicine. Nuclear Medicine Communications. June 2018;39(6):500–4.

46. Rizzo A, Annunziata S, Salvatori M. Side effects of theragnostic agents currently employed in clinical practice. Q J Nucl Med Mol Imaging [Internet]. February 2022 [accessed 21. March 2022];65(4). Available under: https://www.minervamedica.it/index2.php?show=R39Y2021N04A0315

47. Strigari L, Konijnenberg M, Chiesa C, Bardies M, Du Y, Gleisner KS, et al. The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy. Eur J Nucl Med Mol Imaging. October 2014;41(10):1976–88.

48. Juget F, Talip Z, Nedjadi Y, Durán MT, Grundler PV, Zeevaart JR, et al. Precise activity measurements of medical radionuclides using an ionization chamber: a case study with Terbium-161. EJNMMI Phys. December 2022;9(1):19.

49. Busemann Sokole E, Płachcínska A, Britten A, EANM Physics Committee. Acceptance testing for nuclear medicine instrumentation. Eur J Nucl Med Mol Imaging. March 2010;37(3):672–81.

50. Protection R. 161. Criteria for Acceptability of Medical Radiological Equipment used in Diagnostic Radiology. Nuclear Medicine and Radiotherapy. 2012;

51. Kaalep A, Sera T, Rijnsdorp S, Yaqub M, Talsma A, Lodge MA, et al. Feasibility of state of the art PET/CT systems performance harmonisation. Eur J Nucl Med Mol Imaging. July 2018;45(8):1344–61.

52. Larsson E, Brolin G, Cleton A, Ohlsson T, Lindén O, Hindorf C. Feasibility of Thorium-227/Radium-223 Gamma-Camera Imaging During Radionuclide Therapy. Cancer Biotherapy and Radiopharmaceuticals. 1. September 2020;35(7):540–8.

53. Benabdallah N, Scheve W, Dunn N, Silvestros D, Schelker P, Abou D, et al. Practical considerations for quantitative clinical SPECT/CT imaging of alpha particle emitting radioisotopes. Theranostics. 2021;11(20):9721–37.

54. Tran-Gia J, Denis-Bacelar AM, Ferreira KM, Robinson AP, Calvert N, Fenwick AJ, et al. A multicentre and multi-national evaluation of the accuracy of quantitative Lu-177 SPECT/CT imaging performed within the MRTDosimetry project. EJNMMI Phys. December 2021;8(1):55.

55. Rydén T, Heydorn Lagerlöf J, Hemmingsson J, Marin I, Svensson J, Båth M, et al. Fast GPU-based Monte Carlo code for SPECT/CT reconstructions generates improved 177Lu images. EJNMMI Phys. December 2018;5(1):1.

56. Marin I, Rydèn T, Van Essen M, Svensson J, Gracheva N, Köster U, et al. Establishment of a clinical SPECT/CT protocol for imaging of 161Tb. EJNMMI Phys. December 2020;7(1):45.

57. van der Meulen NP, Strobel K, Lima TVM. New Radionuclides and Technological Advances in SPECT and PET Scanners. Cancers. 8. December 2021;13(24):6183.

58. Desy A, Bouvet GF, Frezza A, Després P, Beauregard J-M. Impact of dead time on quantitative 177Lu-SPECT (QSPECT) and kidney dosimetry during PRRT. EJNMMI Phys. December 2020;7(1):32.

59. Jha AK, Mithun S, Rangarajan V, Wee L, Dekker A. Emerging role of artificial intelligence in nuclear medicine. Nuclear Medicine Communications. June 2021;42(6):592–601.

60. Ljungberg M, Sjögreen Gleisner K. Personalized Dosimetry for Radionuclide Therapy Using Molecular Imaging Tools. Biomedicines. 15. November 2016;4(4):25.

61. Huizing DMV, Peters SMB, Versleijen MWJ, Martens E, Verheij M, Sinaasappel M, et al. A head-to-head comparison between two commercial software packages for hybrid dosimetry after peptide receptor radionuclide therapy. EJNMMI Phys. December 2020;7(1):36.

62. Della Gala G, Bardiès M, Tipping J, Strigari L. Overview of commercial treatment planning systems for targeted radionuclide therapy. Physica Medica. December 2021;92:52–61.

63. Danieli R, Milano A, Gallo S, Veronese I, Lascialfari A, Indovina L, et al. Personalized Dosimetry in Targeted Radiation Therapy: A Look to Methods, Tools and Critical Aspects. JPM. 2. February 2022;12(2):205.

64. Lodge MA, Holt DP, Kinahan PE, Wong DF, Wahl RL. Performance assessment of a NaI(Tl) gamma counter for PET applications with methods for improved quantitative accuracy and greater standardization. EJNMMI Phys. December 2015;2(1):11.

65. Lassmann M, Chiesa C, Flux G, Bardiès M, EANM Dosimetry Committee. EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting. Eur J Nucl Med Mol Imaging. January 2011;38(1):192–200.

66. Gear JI, Cox MG, Gustafsson J, Gleisner KS, Murray I, Glatting G, et al. EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations. Eur J Nucl Med Mol Imaging. December 2018;45(13):2456–74.

67. Uribe C, Peterson A, Van B, Fedrigo R, Carlson J, Sunderland J, et al. An International Study of Factors Affecting Variability of Dosimetry Calculations, Part 1: Design and Early Results of the SNMMI Dosimetry Challenge. J Nucl Med. December 2021;62(Supplement 3):36S-47S.

68. Lawhn-Heath C, Hope TA, Martinez J, Fung EK, Shin J, Seo Y, et al. Dosimetry in radionuclide therapy: the clinical role of measuring radiation dose. The Lancet Oncology. February 2022;23(2):e75–87.

69. Koziorowski J, Behe M, Decristoforo C, Ballinger J, Elsinga P, Ferrari V, et al. Position paper on requirements for toxicological studies in the specific case of radiopharmaceuticals. EJNMMI radiopharm chem. January 2017;1(1):1.

70. Korde A, Mikolajczak R, Kolenc P, Bouziotis P, Westin H, Lauritzen M, et al. Practical Considerations for Navigating the Regulatory Landscape of Non-Clinical Studies for Clinical Translation of Radiopharmaceuticals. EJNMMI Radiopharmacy & Chemistry. 2022;submitted

71. Todde S, Windhorst AD, Behe M, Bormans G, Decristoforo C, Faivre-Chauvet A, et al. EANM guideline for the preparation of an Investigational Medicinal Product Dossier (IMPD). Eur J Nucl Med Mol Imaging. November 2014;41(11):2175–85.

Appendix 1: Standard template for quality requirements of novel radionuclides

The following table should be a Standard Template for the compilation of specifications of novel radionuclides

Table 6. Standard Template for the compilation of specifications of novel radionuclides

Parameter	Requirements
Form	
Appearance	
Radionuclide identity (half-life)	
Radionuclide identity (gamma spectrometry)	
Radionuclidic purity (gamma spectrometry)	
Chemical purity (ICP-OES)	
Microbiological quality	
Bacterial endotoxin	
pH (pH strips)	
Radioactive concentration (gamma spectrometry)	
Molar activity (as measured by ICP-OES)	
Chemical form	
Production route	
Decay	
Processing	
Primary Container Glass	
Shelf-life	

Appendix 2: Microdosing requirements according to ICH M3 (R2)

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals.

Table 7: Recommended Non-Clinical Studies to Support Exploratory Clinical Trials

Clinical		**Non clinical**		
Dose to be Administered	**Start and Maximum Doses**	**Pharmacology**	**General Toxicity Studies [a]**	**Genotoxicity [b] / Other**
Approach 1: Total dose ≤ 100 µg (no inter-dose interval limitations) AND Total dose ≤ 1/100th NOAEL and ≤1/100th pharmacologically active dose (scaled on mg/kg for *i.v.* and mg/m2 for oral)	Maximal and starting doses can be the same but not exceed a total accumulated dose of 100 µg	*In vitro* target/ receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection.	Extended single dose toxicity study (see footnotes c and d) in one species, usually rodent, by intended route of administration with toxicokinetic data, or via the *i.v.* route. A maximum dose of 1000-fold the clinical dose on a mg/kg basis for *i.v.* and mg/m2 for oral administration can be used.	Genotoxicity studies are not recommended, but any studies or SAR assessments conducted should be included in the clinical trial application. For highly radioactive agents (e.g. PET imaging agents), appropriate PK and dosimetry estimates should be submitted.
Approach 2: Total cumulative dose ≤ 500 µg, maximum of 5 administrations with a washout between doses (6 or more actual or predicted half-lives) AND each dose ≤ 100 µg AND each dose ≤ 1/100th of the NOAEL and ≤ 1/100th of the pharmacologically active dose	Maximal daily and starting doses can be the same, but not exceed 100 µg.	*In vitro* target/receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection.	7-day repeated-dose toxicity study in one species, usually rodent, by intended route of administration with toxicokinetic data, or via the *i.v.* route. Hematology, clinical chemistry, necropsy, and histopathology data should be included. A maximum dose of 1000-fold the clinical dose on a mg/kg basis for *i.v.* and mg/m2 for oral administration can be used.	Genotoxicity studies are not recommended, but any studies or SAR assessments conducted should be included in the clinical trial application. For highly radioactive agents (e.g. PET imaging agents), appropriate PK and dosimetry estimates should be submitted.
Approach 3 Single Dose Studies at Sub-therapeutic Doses or into the Anticipated Therapeutic Range	Starting dose should be based on the types of toxicity findings observed in the most sensitive species and a consideration of the pharmacologically active dose. For other considerations on initial dosing in humans, regional guidance should be consulted. Maximum dose can be that yielding up to ½ NOAEL exposure in the more sensitive species, in	*In vitro* target/receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection. Core battery of safety pharmacology (see Section 2).	Extended single dose toxicity studies in both the rodent and non-rodent (see footnote c) by intended clinical route of administration with toxicokinetics, haematology, clinical chemistry, necropsy, and histopathology data. For this situation the top dose should be MTD, MFD or limit dose (see Section 1.5).	Ames assay (or an alternative assay if Ames is inappropriate, for example, for an antibacterial product).

	cases where any relevant toxicity observed in animals is anticipated to be monitorable and reversible in humans.			
Approach 4: Dosing up to 14 days into the therapeutic range but not intended to evaluate clinical MTD	With toxicity in both species, follow appropriate regional guidance for clinical starting dose. If toxicity is not seen in either species (i.e. the NOAELs are the highest dose tested and doses used were not otherwise limited, e.g. not an MFD), or is seen only in one species, the clinical starting dose should be one that gives a predicted clinical AUC value (based on either interspecies PK modelling or mg/m2 conversion) that is approximately 1/50th of the AUC at the NOAEL from the species yielding the lower When only one species demonstrates toxicity, the exposure. For other considerations on initial dosing in humans, e.g. predicted PD activity, regional guidance should be consulted. Without toxicity in both species, it is recommended that the maximum clinical dose not exceed 1/10th the lower exposure (AUC) in either species at the highest dose tested in the animals.	In vitro target/receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection. Core battery of safety pharmacology (see Section 2) using doses similar to those used for the toxicity studies.	2-week repeated-dose toxicity studies in rodent and non- rodent with standard parameters assessed and where dose selection in animals is based on exposure multiples of anticipated clinical AUC at maximum dose.	Ames assay (or an appropriate alternative assay if Ames is inappropriate, for example, for an antibacterial product) and an assay (in vitro or in vivo) capable of detecting chromosomal damage in a mammalian system

Approach 5: Dosing up to 14 days and not to exceed duration of dosing in non-rodent; into therapeutic range but not intended to evaluate clinical MTD.	Starting dose predicted exposures should not exceed 1/50th the NOAEL in the more sensitive species on a mg/m2 basis. For other considerations on initial dosing in humans, regional guidance should be consulted. The maximum exposure in humans should not be higher than the AUC at the NOAEL in the non- rodent species or higher than ½ the AUC at the NOAEL in the rodent species, whichever is lower[e].	*In vitro* target/receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection. Core battery of safety pharmacology (see Section 2) using doses similar to those used for the toxicity studies.	Standard 2-week repeated- dose toxicity study in rodents (with justification of the rodent as an appropriate species). The top dose should be the MTD, MFD or limit dose (see Section 1.5). Confirmatory study in non-rodent (n=3) at the anticipated NOAEL exposure in rodent, with duration of a minimum of 3 days and at least the intended clinical study duration. Alternatively, an escalating dose study in the non-rodent with duration of a minimum of 3 days and at least the intended clinical study duration at the anticipated NOAEL exposure in the rodent.	Ames assay (or an appropriate alternative assay if Ames is inappropriate, for example, for an antibacterial product) and an assay (*in vitro* or *in vivo*) *capable of detecting chromosomal damage in a mammalian system. If an* in vivo *assessment is used then this could be part of the rodent toxicity study.*

a) General toxicity studies should be conducted according to GLP regulations.
b) See ICH Topic S2B Document "Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals".
c) Generally, extended single dose toxicity studies should be designed to evaluate hematology, clinical chemistry, necropsy, and histopathology data (control and high dose only if no treatment-related pathology is seen at the high dose) after a single administration, with further evaluations conducted 2 weeks later to assess delayed toxicity and/or recovery. The usual design for rodents consists of 10 animals/sex/group to be assessed on the day following dosing, and 5 animals/sex at the dose level(s) selected to be assessed on day 14 post-dose. The usual design for non-rodents consists of 3/sex/group for all groups on day 2 and 2/sex for the dose level(s) assessed on day 14.
d) A single dose level to assess reversibility/delayed toxicity on day 14 can support the microdose approach. The dose level used need not be the high dose but should be a dose that is at least 100 times the clinical dose.
e) In the absence of adverse effects in the clinical trial, escalation above this AUC can be appropriate if the findings in the toxicity studies are anticipated to be monitorable, reversible, and of low severity in humans.