Perspectives of international organisations: International Atomic Energy Agency

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RCRT Section in IAEA Organization Chart

- **OFFICE OF DIRECTOR GENERAL**
  - Department of Management
  - Department of Nuclear Energy
  - **DEPARTMENT OF NUCLEAR SCIENCE & APPLICATION**
    - **Division of Physical & Chemical Sciences**
      - **Radiochemistry & Radiation Technology Section (RCRT)**
  - Department of Technical Cooperation
  - Department of Nuclear Safety and Security
  - Department of Safeguards

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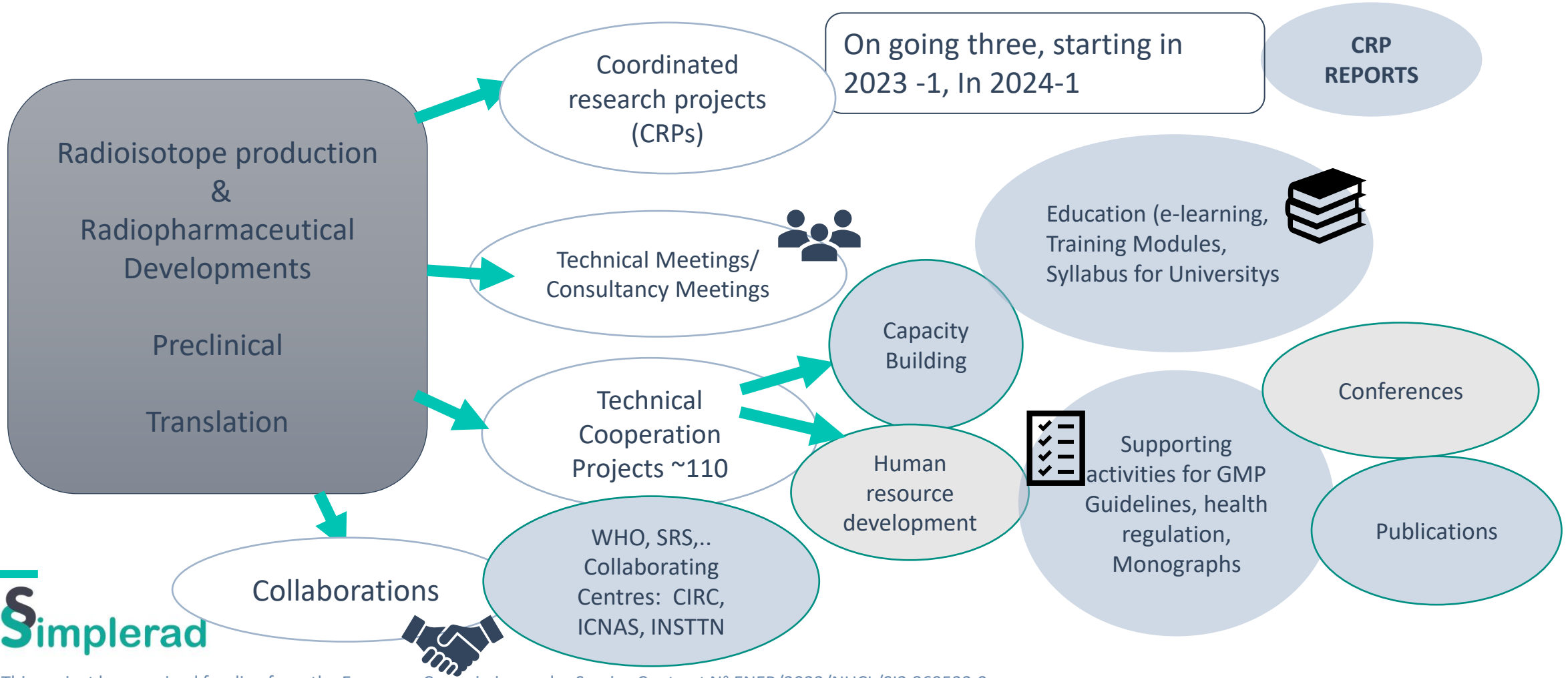
IAEA Activities in radiopharmaceuticals

- To support Member States for Radioisotope and radiopharmaceutical production to ensure availability of safe and effective products of appropriate quality for patients use



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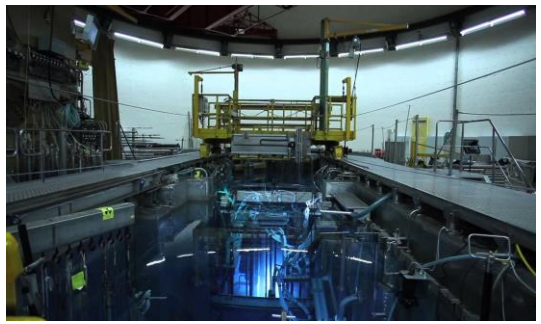
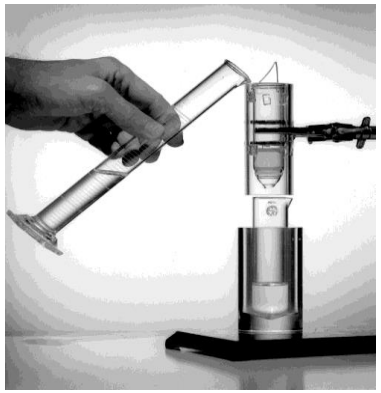
How RPh were prepared historically? what changed today- regulations???

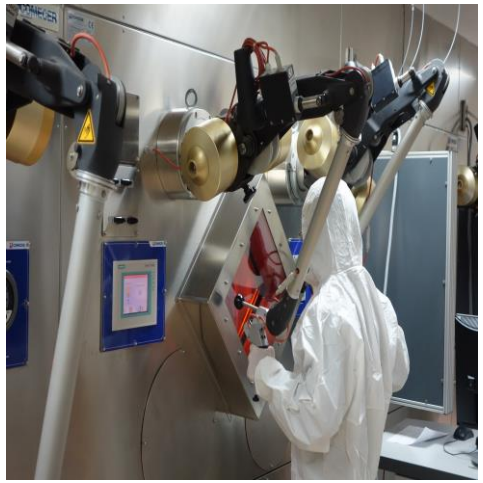


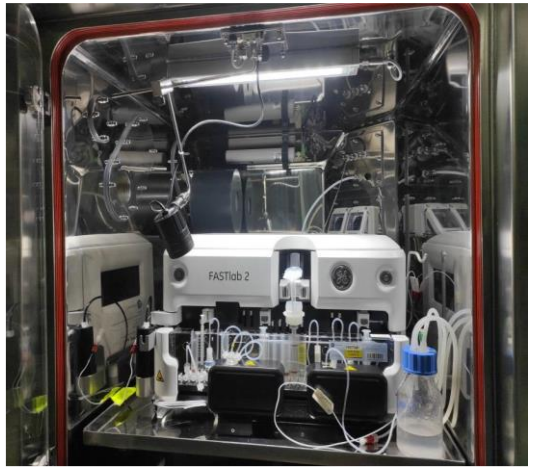
Use of I-131 for treatment since early 1940's



Original Tc-99m generator 1958 shown without shielding

Initial synthesis module for [^{18}F] FDG





Some examples of recent facilities established through IAEA Technical cooperation Projects in radiopharmaceutical area

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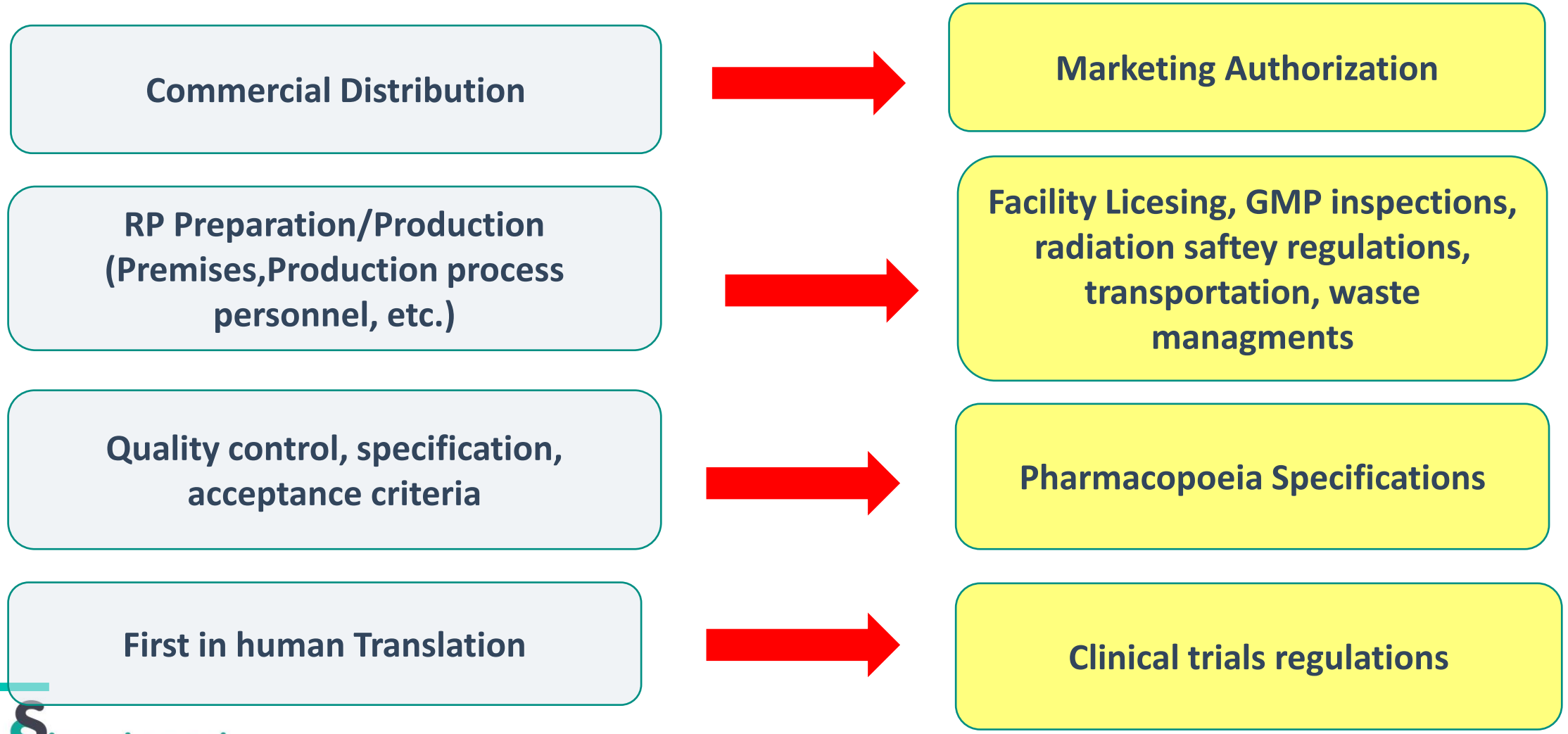
What is regulated for Radiopharmaceuticals



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IAEA-RPRC Activities in radiopharmaceuticals regulations

- Regulatory basis for the use of radiopharmaceuticals
  - Marketing authorization
  - **The small scale, non-commercial preparation of radiopharmaceuticals : Compounding, Magistral preparation Extemporaneous Preparation**
  - Clinical trials
- There are several factors that contribute to making the access to RPs challenging, and amongst them, the pharmaceutical regulatory framework and associated guidelines play a very important role in many ways.
- We receive several requests from MS to support capacity building and guidance for effective implementation of radiopharmaceutical oversight
  - Regional and national projects cover RP regulation activities, enabling conducting training programs, fellowships, expert mission
  - Specific Technical Meetings for Health regulations of RPH were conducted in 2017, 2023
  - Collaborations with WHO for International Pharmacopoeia and guidelines

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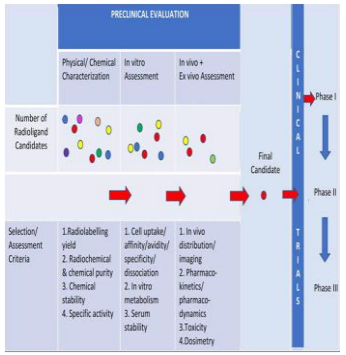
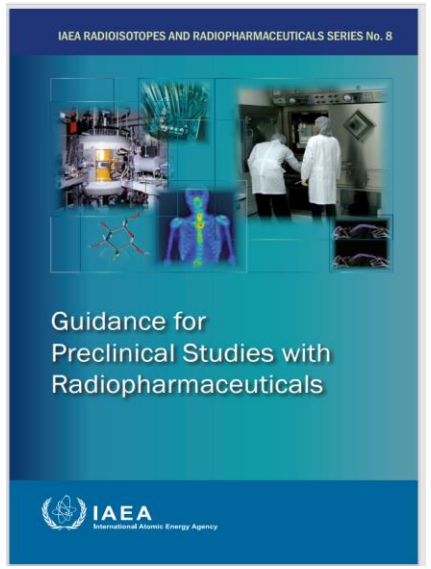
IAEA Guidelines for Preclinical studies for Radiopharmaceuticals

- Preclinical evaluation is an integral part of the development of any drug, including radiopharmaceuticals.
- Different in vitro techniques are required to ascertain the biological properties of radiolabelled molecules in order to obtain approval for testing in laboratory animals.
- In many instances, its necessary to determine safety and efficacy of the new radiopharmaceutical products by suitable animal studies prior to translation for clinical trials

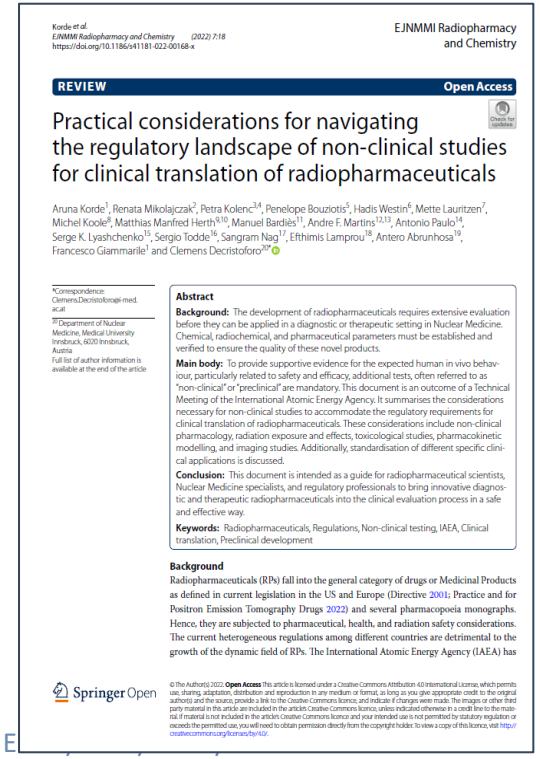




[Guidance for Preclinical Studies with Radiopharmaceuticals | IAEA]

The IAEA Conducted Technical Meeting on Non-clinical testing of radiopharmaceuticals: regulatory consideration Nov 2021

The report is published in *EJNMMI radiopharm. chem. 7, 18 (2022). https://doi.org/10.1186/s41181-022-00168-x*


Korde et al. EJNMMI Radiopharmacy and Chemistry (2022) 7:18 https://doi.org/10.1186/s41181-022-00168-x

EJNMMI Radiopharmacy and Chemistry

REVIEW Open Access

Practical considerations for navigating the regulatory landscape of non-clinical studies for clinical translation of radiopharmaceuticals

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Abstract

Background: The development of radiopharmaceuticals requires extensive evaluation before they can be applied in a diagnostic or therapeutic setting in Nuclear Medicine. Chemical, radiochemical, and pharmaceutical parameters must be established and verified to ensure the quality of these novel products.

Main body: To provide supportive evidence for the expected human in vivo behaviour, particularly related to safety and efficacy, additional tests, often referred to as "non-clinical" or "preclinical" are mandatory. This document is an outcome of a Technical Meeting of the International Atomic Energy Agency. It summarises the considerations necessary for non-clinical studies to accommodate the regulatory requirements for clinical translation of radiopharmaceuticals. These considerations include non-clinical pharmacology, radiation exposure and effects, toxicological studies, pharmacokinetic modelling, and imaging studies. Additionally, standardisation of different specific clinical applications is discussed.

Conclusion: This document is intended as a guide for radiopharmaceutical scientists, Nuclear Medicine specialists, and regulatory professionals to bring innovative diagnostic and therapeutic radiopharmaceuticals into the clinical evaluation process in a safe and effective way.

Keywords: Radiopharmaceuticals, Regulations, Non-clinical testing, IAEA, Clinical translation, Preclinical development

Background

Radiopharmaceuticals (RPs) fall into the general category of drugs or Medicinal Products as defined in current legislation in the US and Europe (Directive 2001; Practice and for Positron Emission Tomography Drugs 2022) and several pharmacopoeia monographs. Hence, they are subjected to pharmaceutical, health, and radiation safety considerations. The current heterogeneous regulations among different countries are detrimental to the growth of the dynamic field of RPs. The International Atomic Energy Agency (IAEA) has

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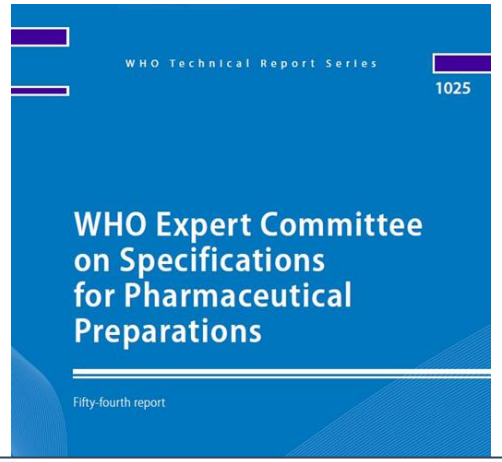
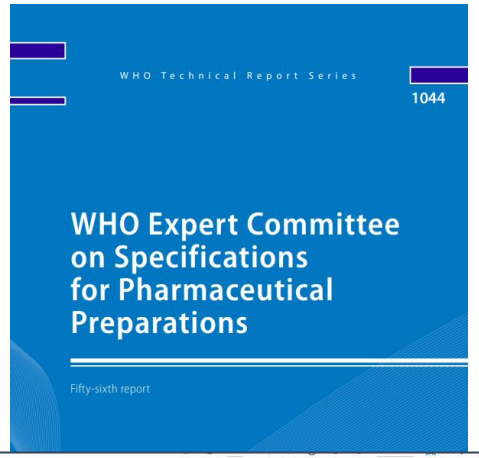
IAEA/ WHO GMP Guidelines for Radiopharmaceuticals





Annex 2

International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products

Acknowledgements

This guideline was prepared by the following experts (in alphabetical order): Mr P.O. Bremer (Norway), Mr C. Fallais (Belgium), Dr S. Kopp (World Health Organization [WHO], Switzerland), Mr P.B. Kulkarni (India), Mr D.V.S. Narasimhan (International Atomic Energy Agency [IAEA], Austria), Mr K.B. Park (Republic of Korea), Dr A. Van Zyl (South Africa), Ms S. Vasanavathana (Thailand) and Mr H. Vera Ruiz (IAEA, Austria).

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Annex 3

IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products

Background

In view of the rapidly expanding field of molecular imaging and targeted radiopharmaceutical therapy, combined with the absence of dedicated guidance specific to the manufacture of investigational radiopharmaceuticals used in both early and late clinical trials, the World Health Organization (WHO), in partnership with the International Atomic Energy Agency (IAEA), has raised the urgency for the generation of a new *IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products.*

The objective of this guideline is to meet current expectations and trends in good manufacturing practices specific to investigational radiopharmaceuticals used in clinical trials (that is, phase I, phase II and phase III trials) and to harmonize the text with the principles from other related international guidelines.

This text was developed in alignment with the *Good manufacturing practices; supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans* (*1*). A draft working

IAEA/WHO·good·manufacturing·practices·for·in-house·cold·kits·for·radiopharmaceutical·preparations¶

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Description·of·Activity¤	Date¤
As· recommended· in· IAEA-WHO· guidelines· on· GMP· for· radiopharmaceutical·products.¤	October·2021¤
Preparation·of·first·draft·working·document.¤	March·2022–May·2023¤
Discussion·of·the·first·draft·working·document·in·a·virtual·meeting· with·an·informal·consultation·group.¤	27–29·June·2023·¤
Preparation·of·working·document·for·public·consultation.¤	July·2023¤
Mailing·of·working·document·to·the·Expert·Advisory·Panel·on·the· International· Pharmacopoeia· and· Pharmaceutical· Preparations· (EAP)·inviting·comments·and·posting·of·the·working·document·on· the·WHO·website·for·public·consultation.¤	July·2023¤
Consolidation· of· comments· received· and· review· of· feedback.· Preparation· of· working· document· for· discussion· and· possible· adoption· by· the· Expert· Committee· on· Specifications· for· Pharmaceutical·Preparations·(ECSPP)¤	September·2023¤
Presentation·to·the·meeting·of·the·ECSPP.¤	9–13·October·2023¤
Any·other·follow-up·action·as·required.¤	TBD¤

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Approved by WHO Expert Committee on Specifications for Pharmaceutical Preparations during their 57th Meeting 9-13 Oct 2023

This project has received funding from the European Comm

TM ‘Pharmaceutical Regulations for Radiopharmaceuticals’ March 2023

The TM held in hybrid-mode had the participation of 37 experts, 11 joining in person and 26 joining on-line. Brought together researchers, regulators, producers, academicians in RPh. Representatives of US-FDA, EMA and other regulatory agencies from different MS, professional Societies: SRS, EANM and WHO

Radiation safety regulations and pharmaceutical/drug oversight are well established in many MS (were not discussed during this TM). whereas establishing pharmaceutical framework for radiopharmaceuticals require special regulatory consideration due to their distinct characteristics than conventional pharmaceutical products

The TM strongly advocated creating an international expert group to provide regulatory guidance on RPs for MS. This will facilitate common understanding of the requirements and their compliance

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Major findings, Observations and take-home message from TM

- Large diversity (heterogenicity) in radiopharmaceutical regulatory management - procedures and practices - as well as underlying legal framework - is noticeable
- Regulation of radiopharmaceuticals should be risk based – the more risk, the more regulatory oversight and manufacturing process controls are required.
- Lack of- or mis-communication between radiation safety and pharmaceutical authorities often results in the lack of availability of certain radiopharmaceuticals or delays in approvals.
- Successful development of new radiopharmaceuticals requires dialog between Investigators and regulators.
- Regulatory Definition of Radiopharmaceuticals (incl. e.g. kits, precursors, generators) are often interpreted differently and result in variations in regulatory requirements.
- Definition of responsibilities and qualification of personnel were also observed to be a major challenge in many MS
- Current status : Position paper in drafting stage, Expert working group establishment is under consideration

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