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Introduction to the current status of pharmaceutical regulation of radiopharmaceuticals and IAEA's efforts

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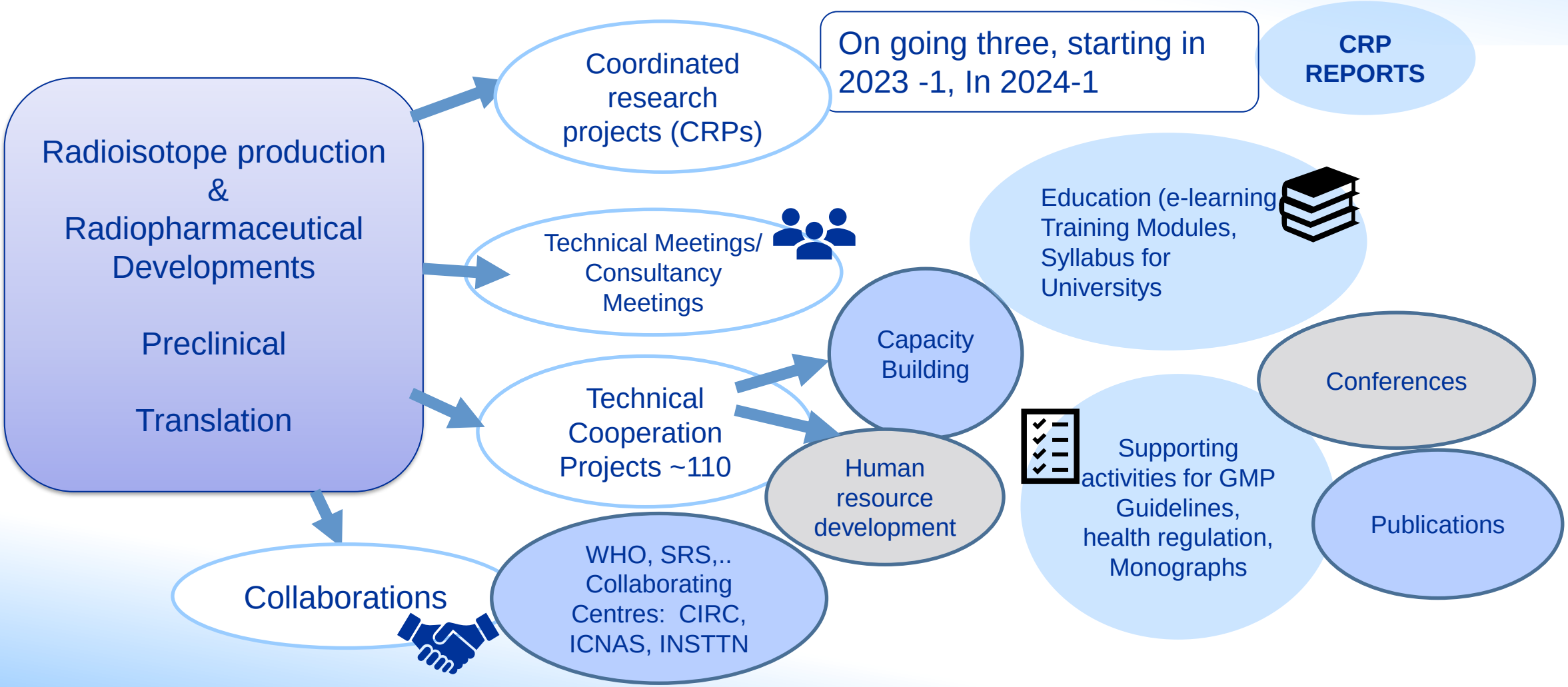
RCRT Section in IAEA Organization Chart

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

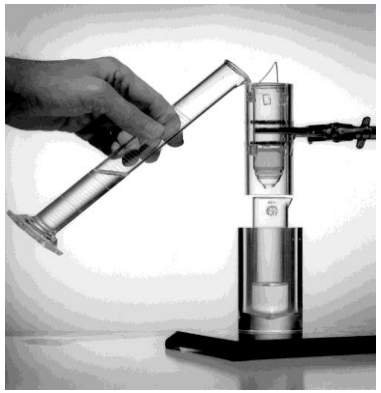
IAEA Activities in radiopharmaceuticals

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



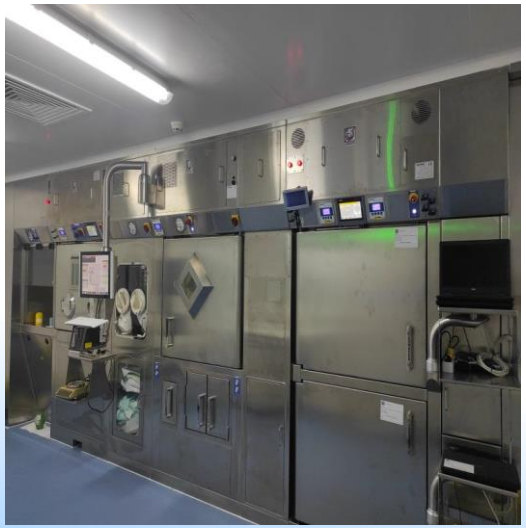
How RPh prepared historically what changed today-regulations???

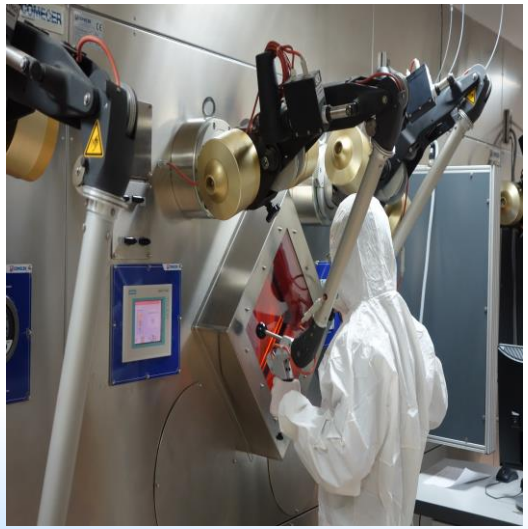
Use of I-131 for treatment since early 1940's

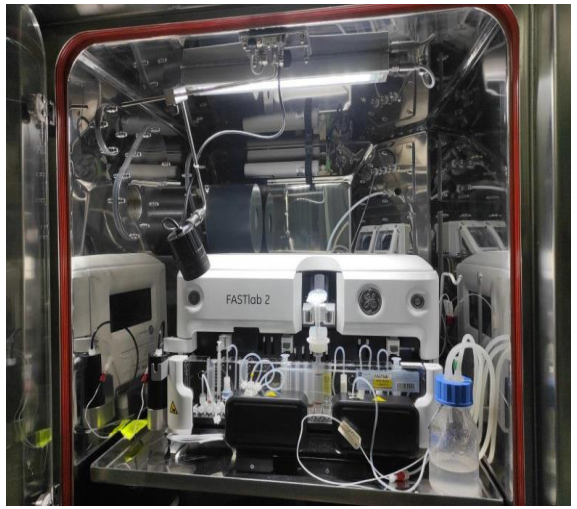


Original Tc-99m generator 1958 shown without shielding

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







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

Radiopharmaceuticals are usually very safe

- Limited shelf life due to associated radionuclide
- Need for local production
- A simple distribution chain,
- One single product is prepared and used in different settings
- Small batch size
- Most of the times QC sample represents whole batch
- Need for parametric release for most RPH products
- Diagnostic RPH have very low potential to exist pharmacological/toxic effects
- Limited market compared to other pharmaceutical products
- Limited availability of formal radiopharmacy education
- Radiation regulations for preparation, handling, transport adherence to ALARA principals
- Heterogeneous situation on regulation practices

In 2004 a critical event occurred: hepatitis C contamination of a radiopharmaceutical kit formulation compounded at a centralized nuclear pharmacy (*8*). This contamination was the result of reusing syringes and 0.9% sodium chloride vials, both of which are single-use products. It also involved the simultaneous preparation of a kit formulation by the same individual who was radiolabeling white blood cells. Two people died, and 16 people tested positive for hepatitis C RNA; all had received doses from the contaminated radiopharmaceutical vial. Though this was not a toxicity issue per se, an event that causes death will lead to increased scrutiny of a field and to increased FDA oversight in general.

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Regulations

- Voluntary Standards
  - Good practice requires education, essential education is often adopted by professional societies and organizations and become voluntary standards.
  - Guidance documents, standards of conduct, reports, articles are all examples of voluntary standards.
  - Voluntary Standards often lack enforcement.
- **Mandatory Standards**
  - **Regulations are mandatory standards, authorized by national or regional law.**
  - **Compliance with these regulations often requires enforcement.**
  - **Enforcement requires legislative authority, i.e. a law or statute. Enforcement often resides in the national authorities.**
  - **Enforcement often, but not always, requires inspections by qualified inspectors.**
- Any regulatory activities should always aim to ensure patient's efficient access to safe and effective products with appropriate quality

Radiopharmaceutical regulations

- Radiopharmaceuticals are usually regulated by two different regulatory agencies
  - A licensing agency for the possession and use of radioactive materials
  - A drug or medicine agency

The International Atomic Energy Agency (IAEA), consistent with its statutory objectives and functions, is strongly engaged, among others, in providing guidance and advice to its member states (MS) on various aspects such as, suitable standards for safe handling and transport of radioactive materials (which includes RPs)

Radiation safety regulations are well established in majority of Member States applicable to radiopharmaceuticals

What is regulated for Radiopharmaceuticals → Ways

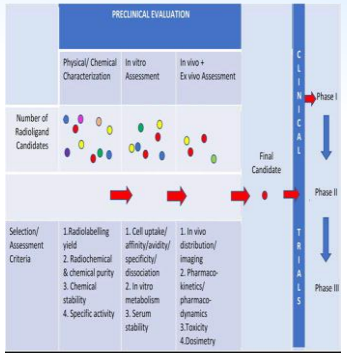
Commercial Distribution	Marketing Authorization
RP Preparation/Production (Premises,Production process personnel, etc.)	Facility Licesing, GMP inspections, radiation saftey regulations, transportation, waste managments
Quality control, specification, acceptance criteria	Pharmacopoeia Specifications
First in human Translation	Clinical trials regulations

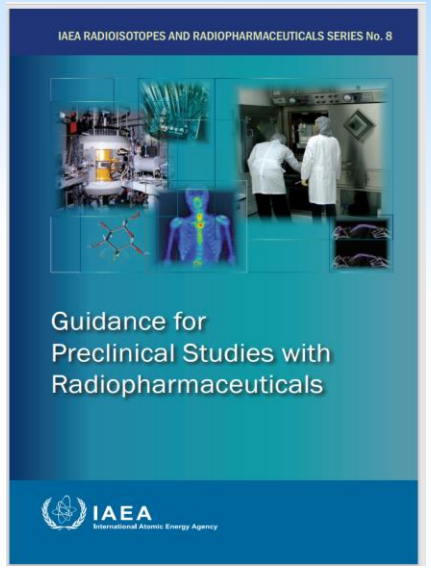
IAEA Activities in radiopharmaceuticals regulations

- 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

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

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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.

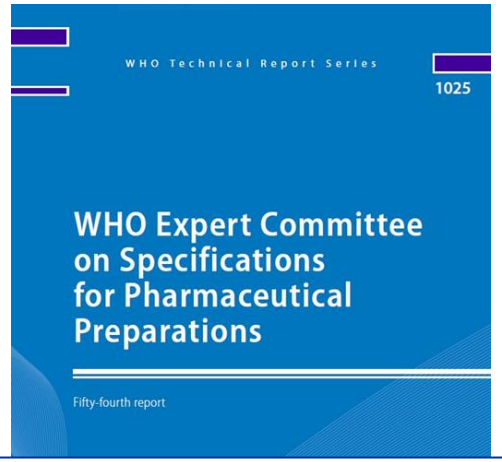
Conclusion: This document is intended as a guide for radiopharmaceutical scientists, Nuclear Medicine specialists, and regulatory professionals to bring innovative diagnostic and therapeutic radiopharmaceuticals into the clinical evaluation process in a safe and effective way.

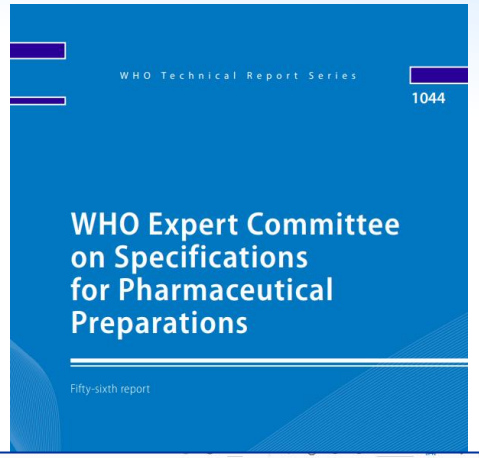
Keywords: Radiopharmaceuticals, Regulations, Non-clinical testing, IAEA, Clinical translation, Preclinical development

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

IAEA/ WHO GMP Guidelines for Radiopharmaceuticals





Annex 2

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

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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

Pharmaceutical Regulatory agencies For RPh in MS other than US and EU

Country	Pharmaceutical regulatory agency
Australia	Therapeutic Goods Administration TGA
Azerbaijan	Medical Department State Agency on Nuclear and Radiological Activitirs Regulation, Ministry of Emergency Situations of Azerbaijan Republic
China	China National Institutes for Food and Drug Control (NIFDC)
Brazil	Brazilian Health Surveillance Agence(ANVISA)
Columbia	Drugs and Technologies Ministry of Health and Social Protection
Cuba	Medical Physics Section, State Control of Drugs and Medical Devices (CECMED)
India	Central Drug standard Control Organization (CDSCO) and Radiopharmaceutical Committee of Department of Atomic Energy (DAE)
Indonesia	Indonesian FDA and BAPETEN
Iran	Food and Drug Administration, Iran
Macedonia	Director of Macedonian Agency for Medicines and Medical Devices (MALMED)
Morocco	Directorate of medicine and pharmacy- DMP (Ministry of health)
Philippines	Food and Drug Administration Philippines
Peru	Director General de Medicamentos (DIGIMED) Drugs and Technologies
Sweden	Inspector Industry and Healthcare Medical Products Agency
South Africa	SAHPRA (including radiation control), Pharmacy council for hospital radiopharmacy
Uruguay	Department of Pharmaceuticals in the Ministry of Health

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

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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The conditions of conquest are easy. We have but to toil awhile, endure awhile, believe always, and never turn back