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Atoms for Peace and Development

Trends in Medical Radioisotopes and Radiopharmaceuticals and the role of the IAEA

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2024 Study Panel of the Forum for Nuclear Cooperation in Asia (FNCA),
11. March 2024

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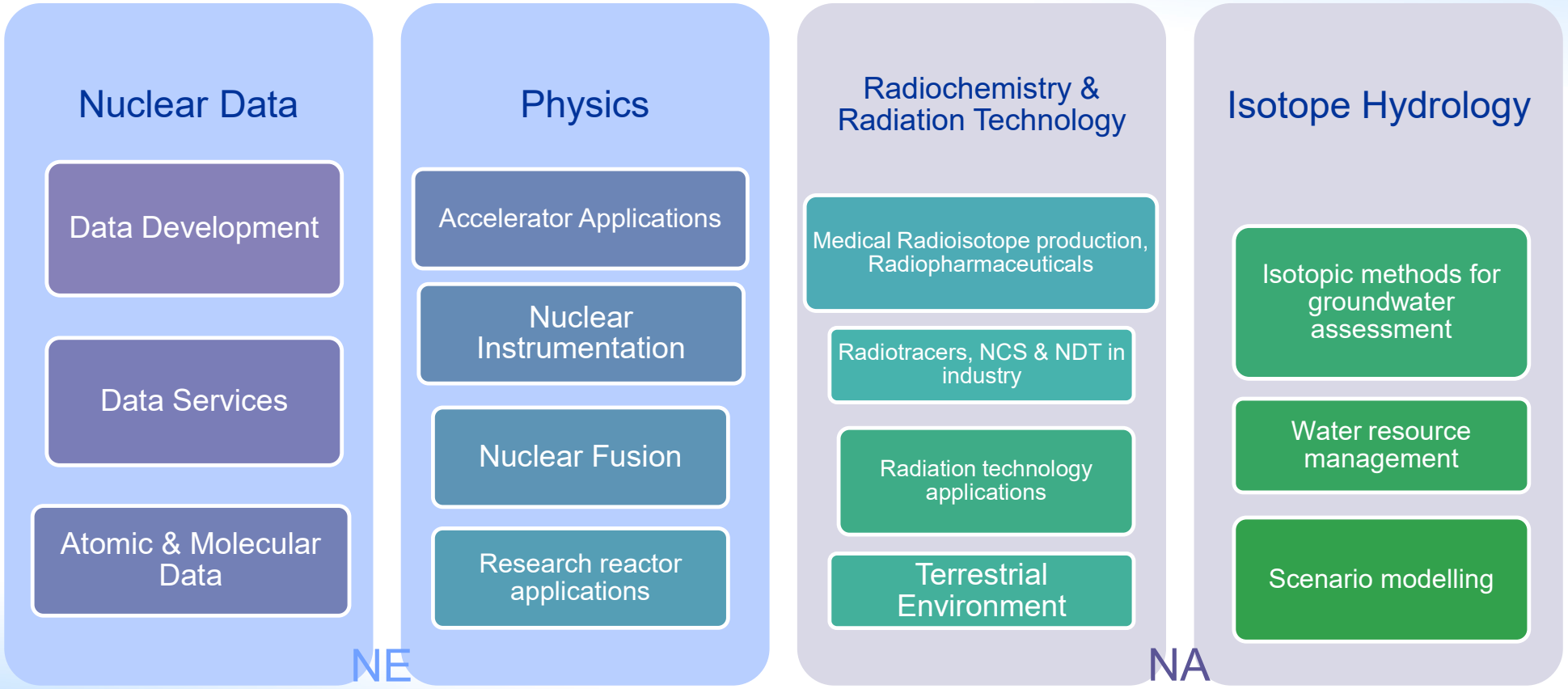

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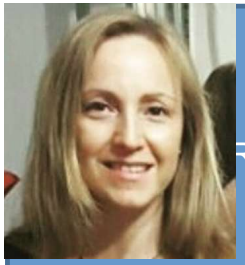

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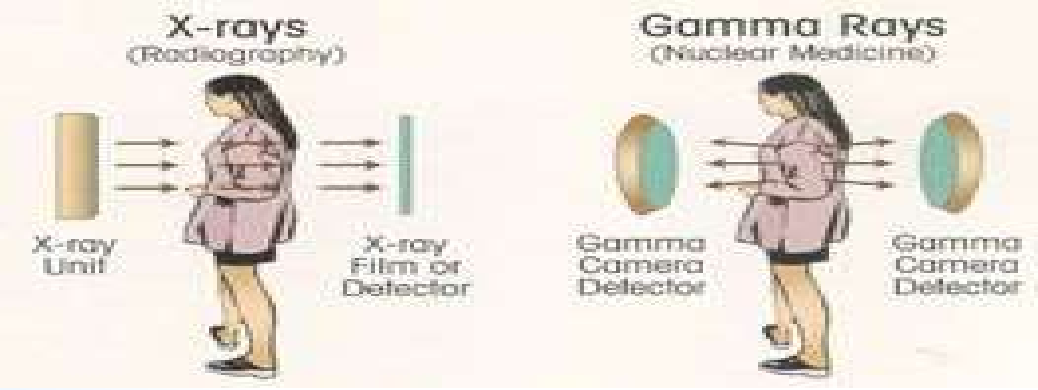
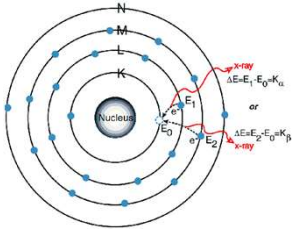
Radiopharmaceuticals: Indispensable components of any nuclear medicine procedure

- In imaging modalities such as ultrasound, CT and MR, the quality of the image depends on the quality of the machine.
- In Nuclear Medicine, the quality of the image depends on the radiopharmaceuticals and the machine



- Radiopharmaceuticals
  - Pharmaceutical products containing one or more radionuclides (radioisotopes) for medicinal purpose
  - Are a safe and effective way to deliver suitable radionuclides inside the body for diagnostic/therapeutic applications



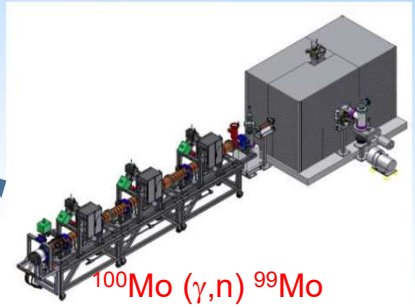
+ Various types of carrier molecules
  - Small molecules: Sugar derivatives, AA, drug
  - peptides, Enzyme inhibitors, Proteins, antibodies etc.

In suitable formulation

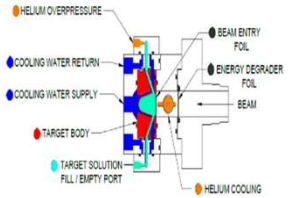
Radioisotope production

$^{18}O(p,n)^{18}F$
$^{89}Y(p,n)^{89}Zr$

Cyclotrons / Accelerators



$^{100}Mo\ (\gamma,n)\ ^{99}Mo$



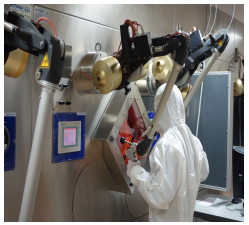
Target Design

PRODUCTION OF RADIOISOTOPES

- Feasibility
- Cost
- Reliability of supply
- Quality

Radionuclidic Purity
Specific activity

Processing



Radionuclide generator

$^{99}Mo/^{99m}Tc$
$^{68}Ge/^{68}Ga$

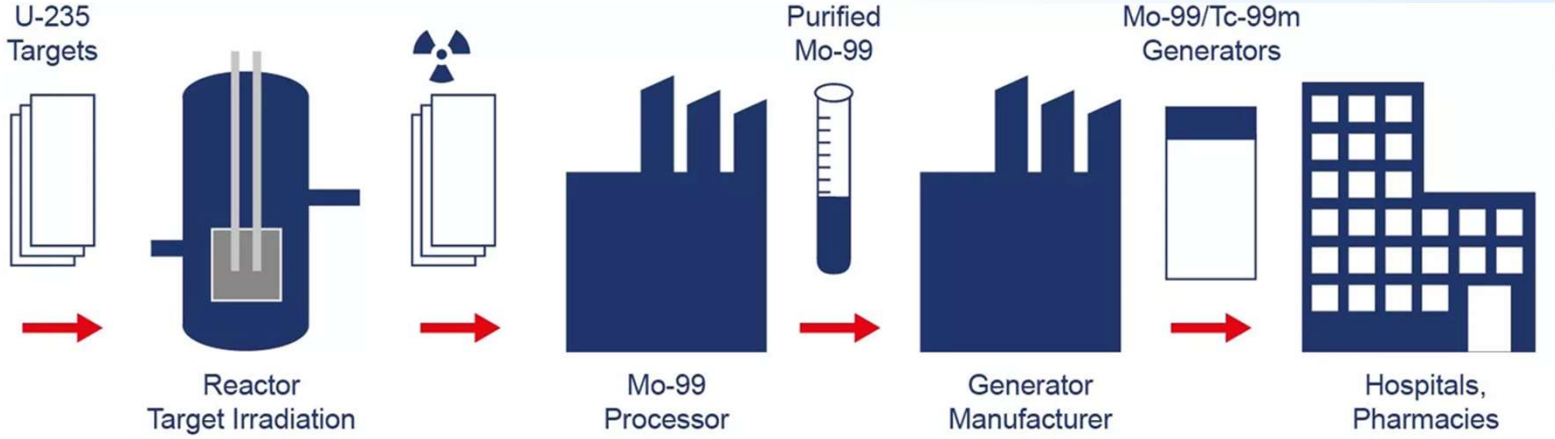
Quality Control

Research Reactor

$^{235}U(n,\ fission) \rightarrow {}^{99}Mo$
$^{176}Lu\ (n,\gamma)^{177}Lu$
$^{130}Te\ (n,\gamma)\ ^{131}Te \longrightarrow {}^{131}I$

Molybdenum- 99/ Technetium-99m: key radioisotopes for Nuclear Medicine

Technetium-99m is diagnostic nuclear medicine work horse, hence availability from pharmaceutical grade Mo-99/Tc-99m generators in hospitals.



- Requires continuous production and co-ordination with generator producers and irradiation facilities.
- Current reactors are aging.
- Unplanned shutdowns/long maintenance disrupt supply chain.
- Alternate methods for Mo-99 or Tc-99m production are needed.

IAEA Coordinated Research Projects addressing:

-Direct cyclotron production of Tc-99m: *'Accelerator-based Alternatives to Non-HEU Production of Mo-99 /Tc-99m'* (2015)

-Photonuclear production of Mo-99 and development of alternate generators for utilization of low –medium specific activity Mo-99: *'New Ways of Producing Tc-99m and Tc-99m Generators'* (2022)

CURRENT GLOBAL Mo-99 / Tc-99m SUPPLY CHAIN

Main supply 6 research reactors

- BR2 (Belgium)
- HFR (The Netherlands)
- MARIA (Poland)
- LVR-15 (Czech Republic)
- SAFARI (South Africa)
- OPAL (Australia)

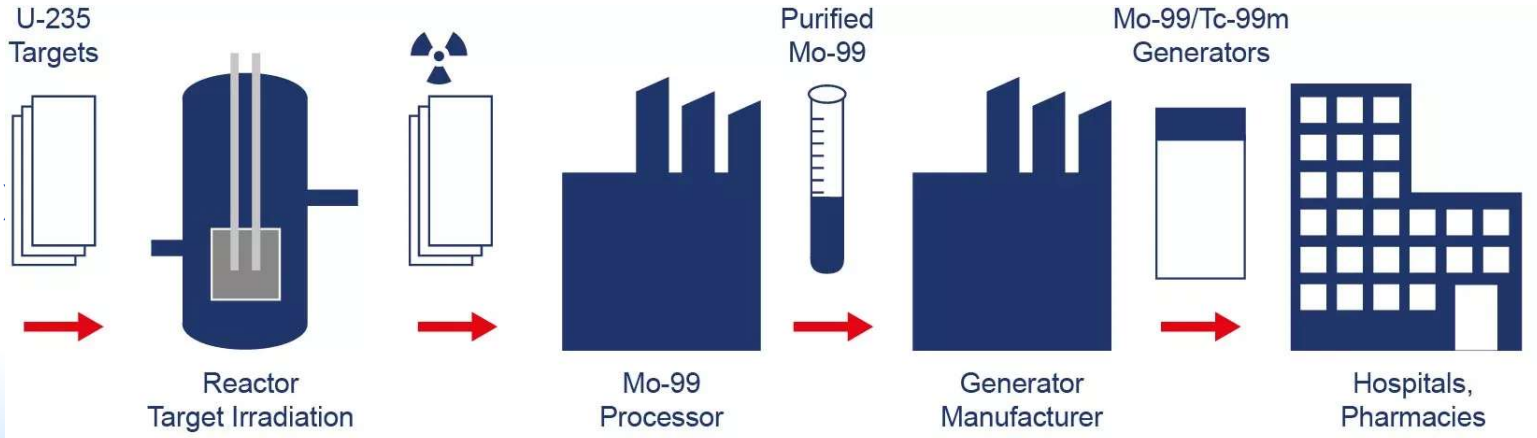
5 processors

- IRE (Belgium)
- CURIUM (The Netherlands)
- NTP (South Africa)
- ANSTO (Australia)
- CNEA (Argentina)

Several $^{99}Mo/^{99m}Tc$ generator manufacturers

- CURIUM (The Netherlands)
- GE-HEALTHCARE (UK)
- LANTHEUS (US)
- MONROL (Turkey)
- POLATOM (Poland)
- …

- **Additional supply**
  - RA-3 (Argentina)
  - RMB (Brazil)
  - FRM-II (Germany)
  - JHR (France)
  - OPG Darlington NPP
  - PALLAS (The Netherlands)
  - MYRRHA (Belgium)
  - ETRR-2 (Egypt)
  - KJRR (South Korea)
  - ...



Various Methods of Mo-99 Production

JSC Isotope

Curium, IRE, NTP, ANSTO

NorthStar, BWXT

Niowave, Lighthouse

NorthStar, Canadian Light Source
GMIS

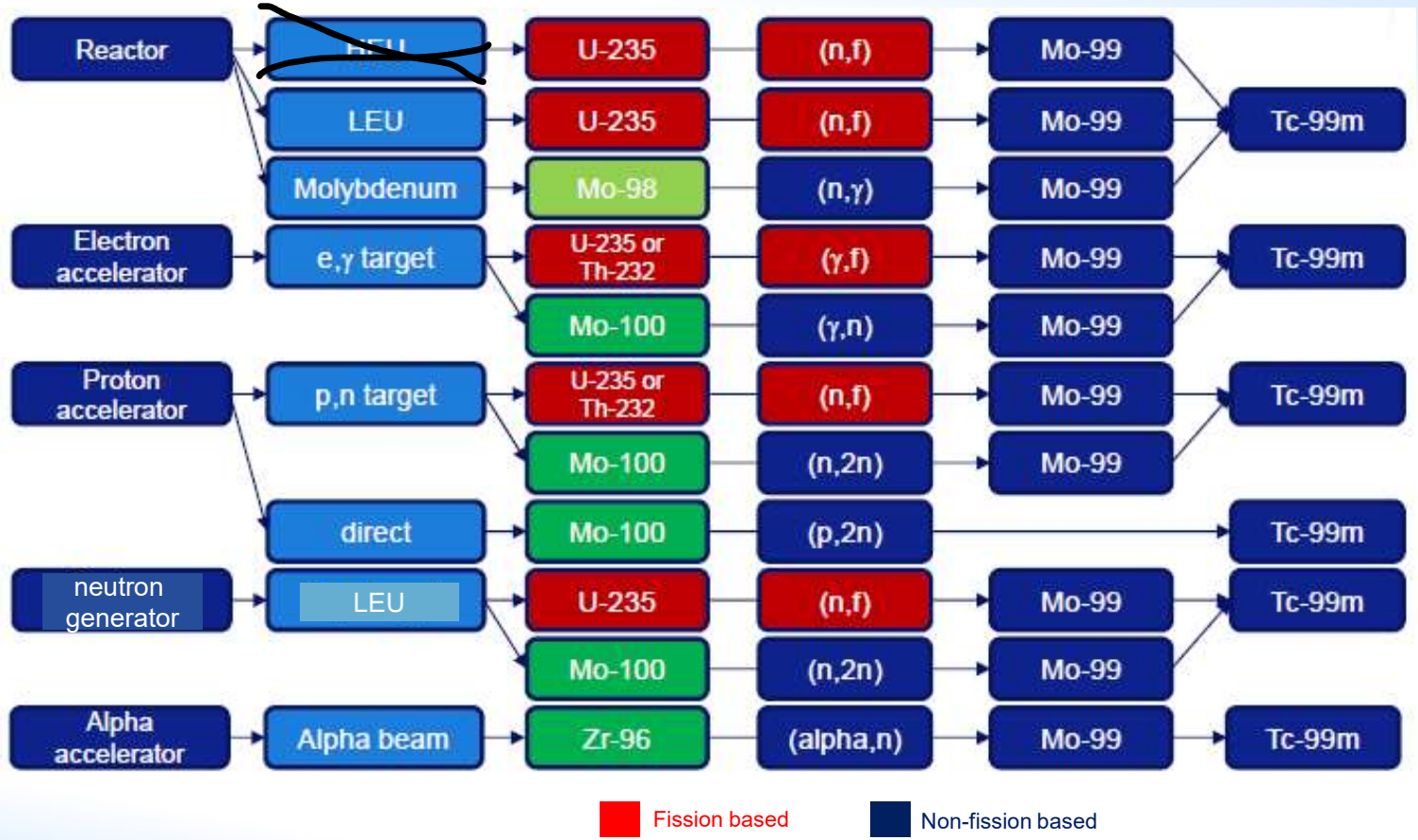
Only experimental

Alliance, CII, ARTMS

SHINE

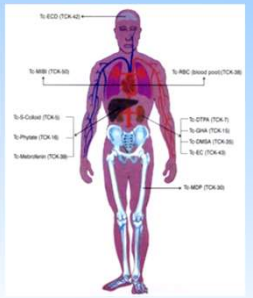
Only Experimental

Alpha Source, LLC



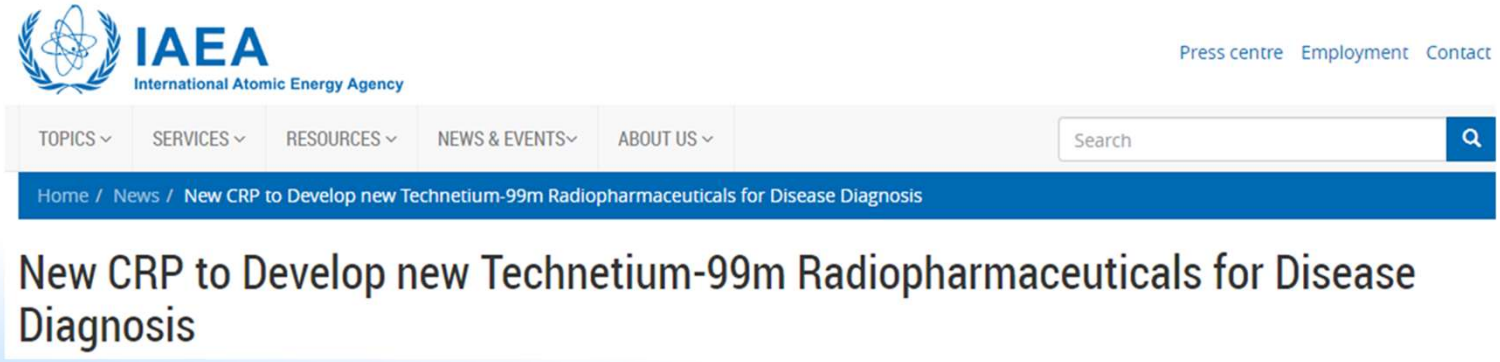
Preparation of Tc-99m Radiopharmaceuticals

Cold kit



Operation level 2a Radiopharmacy : The preparation of radiopharmaceuticals using approved reagent kits, generators and radionuclides (closed procedure). IAEA supports technical cooperation projects for the establishment of such radiopharmacy facilities in Member States.

- How does the same ^{99m}Tc gets into different organs? The answer is in Tc-Chemistry. The transition of Tc-99m radiopharmaceuticals from organ to cellular imaging requires complex ligand developments
- Can New generation ^{99m}Tc agents based on i-PSMA, FAPi derivatives be the alternatives to PET diagnostics?

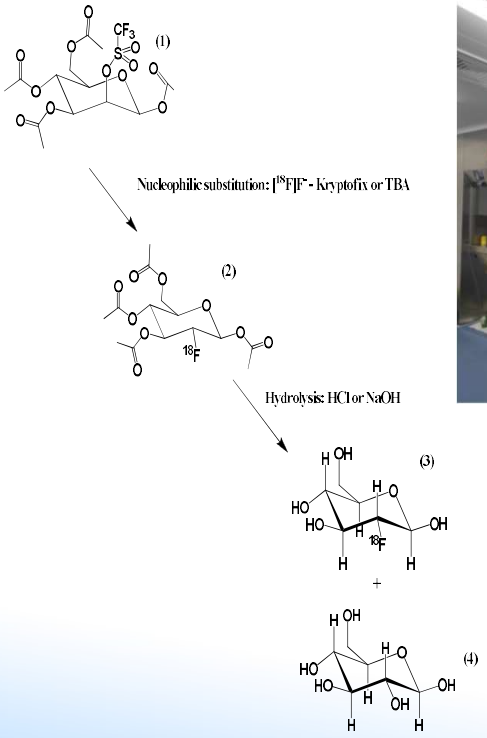


New CRP to Develop new Technetium-99m Radiopharmaceuticals for Disease Diagnosis

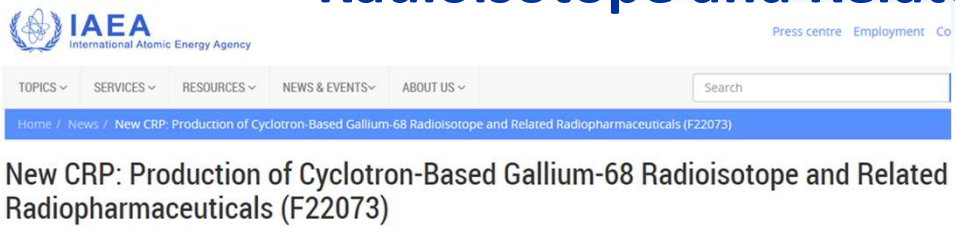
PET Radiopharmaceuticals for Molecular imaging

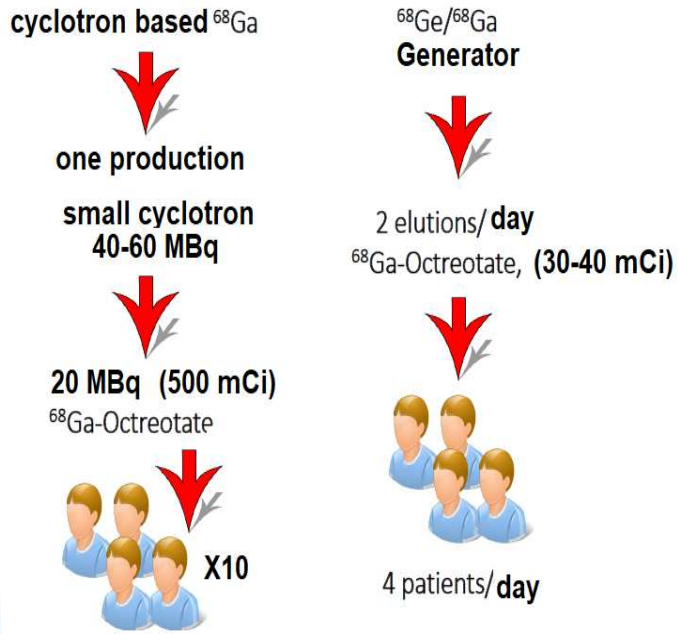
Suitable Carrier molecule labelled with PET Radionuclides mainly ^{18}F, ^{68}Ga, ^{89}Zr, ^{64}Cu etc

Example of success stories of IAEA TC projects for establishment of Radiopharmaceutical production and QC facilities

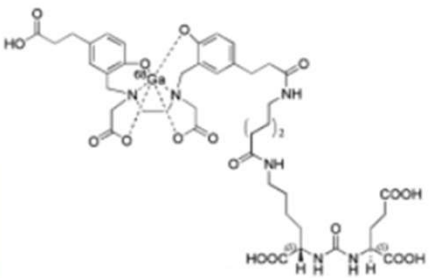


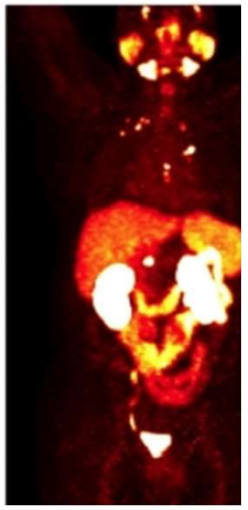
CRP (F22073) Production of Cyclotron-Based Gallium-68 Radioisotope and Related Radiopharmaceuticals





FDA Approved:
- Cyclotron-Produced ^{68}Ga-DOTATOC on October 20,2020
- ^{68}GaPSMA-11 on December 1, 2020





Direct production using cyclotron
- ^{68}Zn (p,n) ^{68}Ga
- Solid target : plate, foil
- Liquid target : $^{68}ZnCl_2$, $^{68}Zn(NO_3)_2$ – dil HNO_3
- Challenges : Targetry, separation chemistry,
- Recycling of target

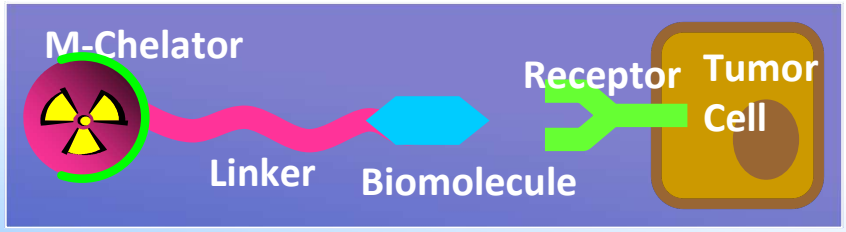
- Next meeting early 2025, 25 official participants from 22 MSs+4 Companies

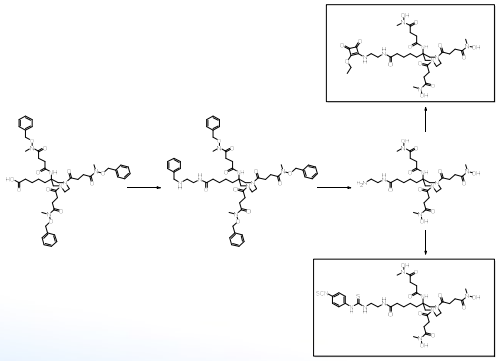
CRP F22071: Production of ^{89}Zr and Development of ^{89}Zr RPhs

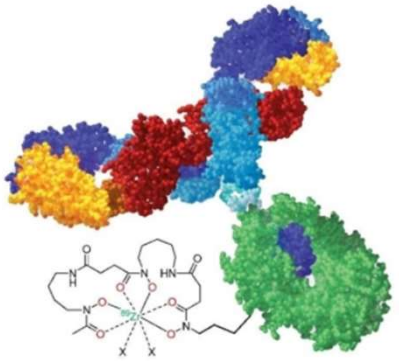
- Half-life of 3.27 d – well suited for study of slower pharmacokinetics e.g antibodies
- CRP: third RCM April 2024

Specific CRP Objectives:

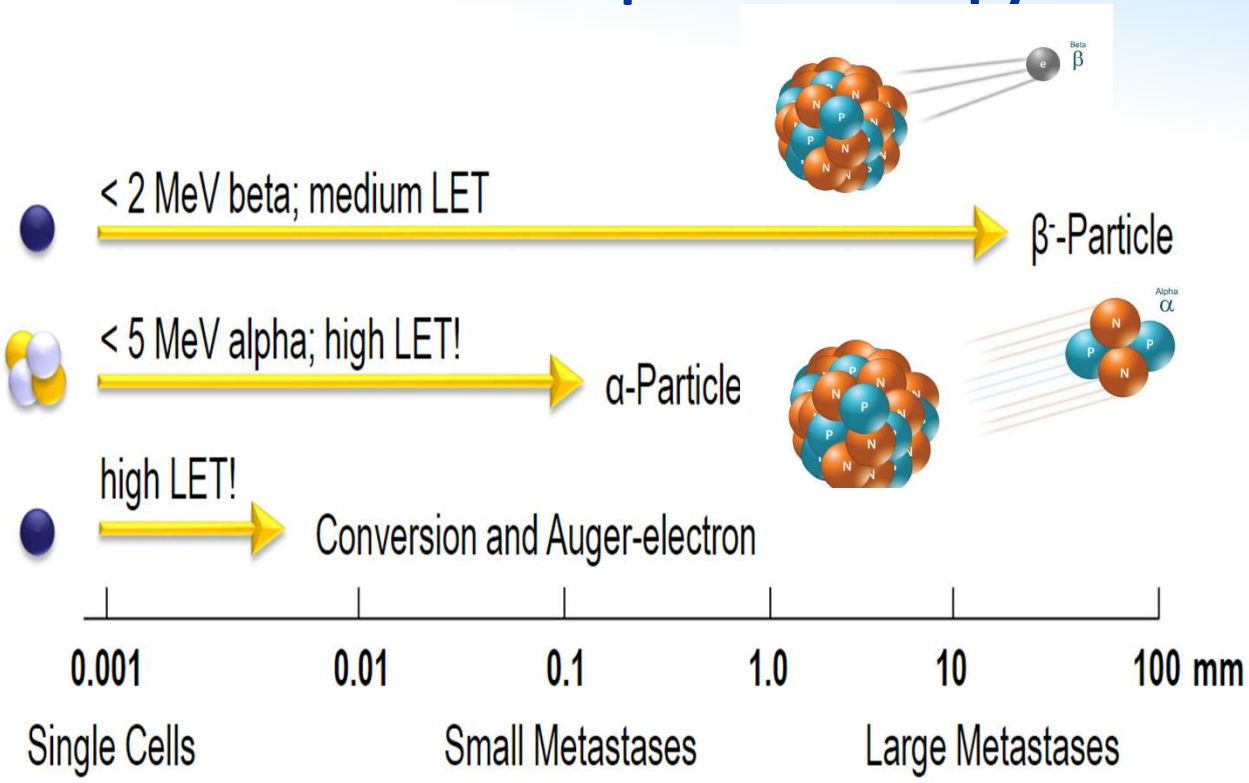
1. Production guidelines for Zr-89 radioisotope using medical cyclotrons
   - Target: easy availability, monoisotopic element, proton beam energy less than 13.3 MeV
   - Standardization of production parameters, separation & purification methods
   - QC of Zr-89
2. Development of Zr-89 radioimmuno molecules and radiolabeled NP and Cells
   - Biomolecule conjugation, radiolabelling, characterization, stability studies & QC
   - In-vitro evaluation, Nonclinical studies & translation

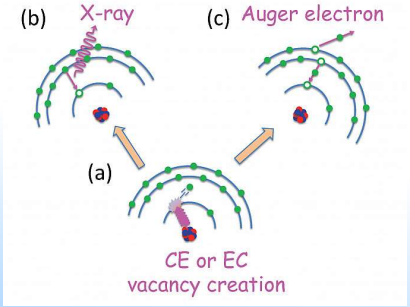






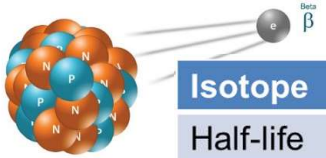
Medical Radioisotopes for therapy





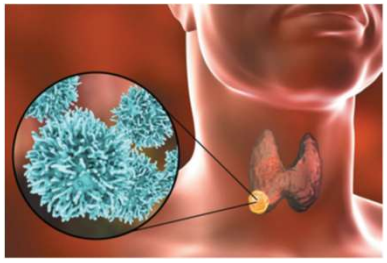
- Foundation was laid more than a century ago for therapy using particle emitters
- Alpha radiation primarily induces DNA double strand breaks
- Alpha induced cell death is largely independent of cell cycle & oxygenation
- Beta emitters suitable for homogenous distribution of dose in large tumours
- Alpha emitters can overcome resistance to beta-, gamma-radiation and chemotherapy
- Suitable for treating bulky diseases

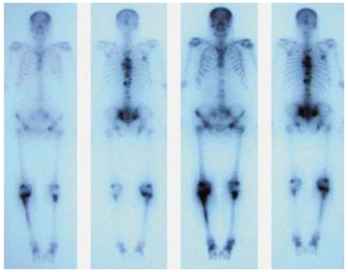
Medical Radioisotopes for therapy

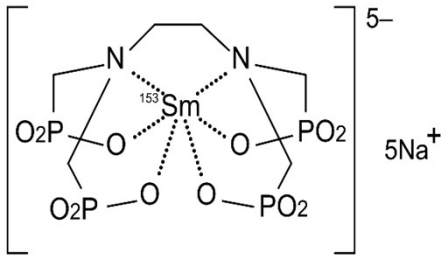


β⁻ emitters

Isotope	^{32}P	^{90}Y	^{153}Sm	^{131}I	^{177}Lu
Half-life	14.3 d	2.7 d	46.3 h	8 d	6.7 d
Production	^{32}S(n,p)^{32}P	Generator (^{90}Sr-^{90}Y) ^{89}Y(n,γ)^{90}Y Fission product	^{152}Sm(n,γ)^{153}Sm enriched	^{130}Te(n,γ)^{131}Te ^{131}Te→^{131}I Fission product	^{176}Lu(n,γ)^{177}Lu ^{176}Yb(n,γ)^{177}Yb ^{177}Yb→^{177}Lu enriched



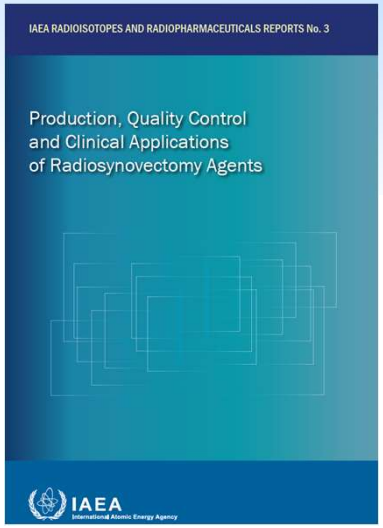


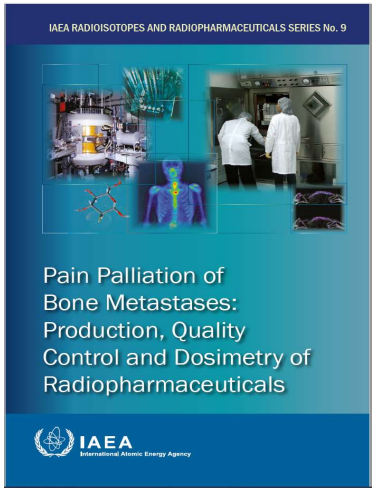


Best example: radioiodines in Thyroid disfunctions/tumours

Diagnostic: I-123, I-124, I-131 iodide and Therapy: I-131 Iodide

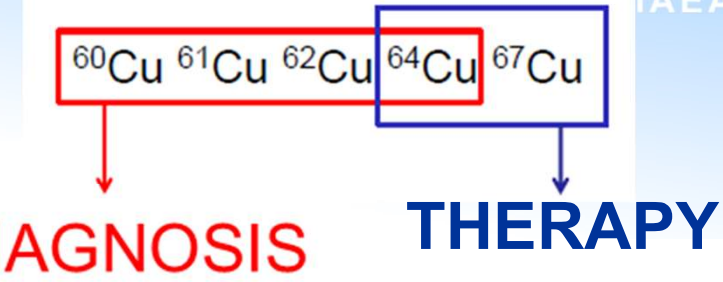
Various bone pain palliative agents : Sm-153 EDTMP, Lu-177 EDTMP, Re-188 HEDP

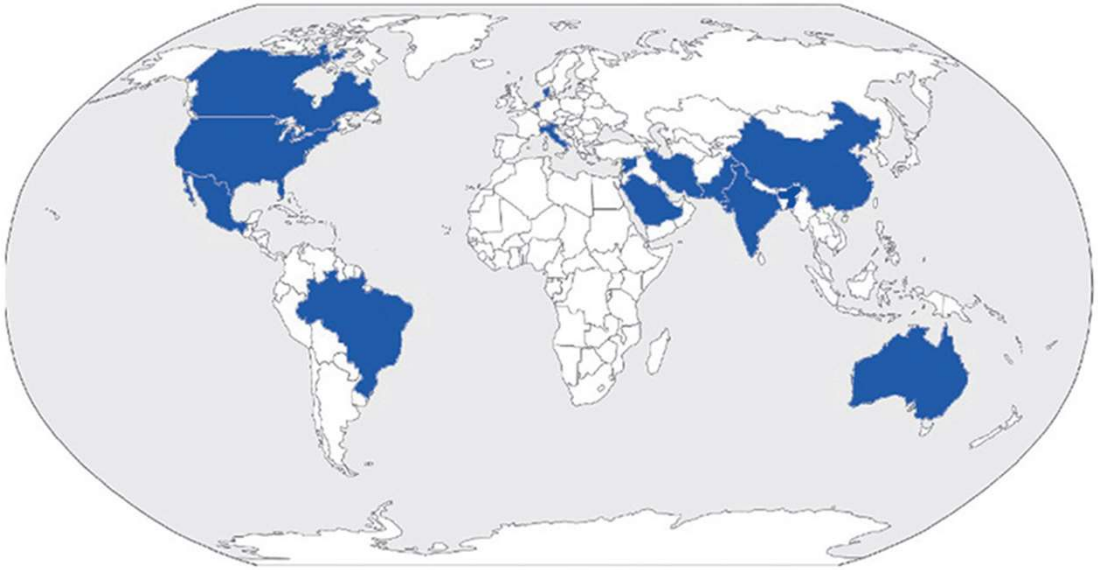


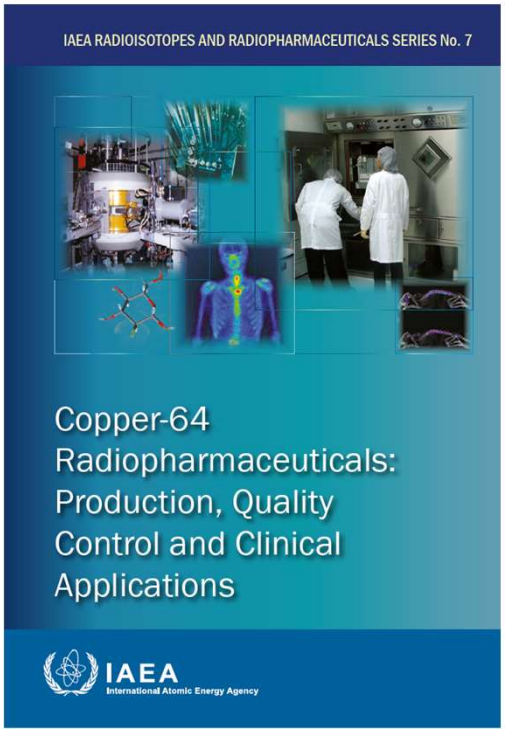


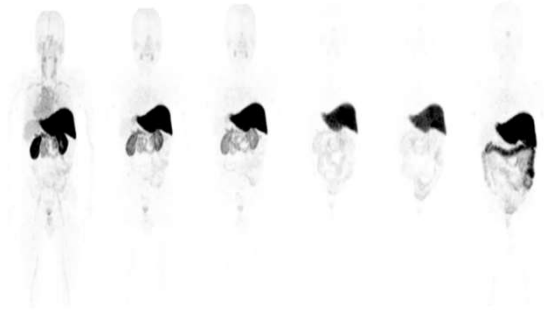
F22067: Copper-64 Radiopharmaceuticals for Theranostic Applications

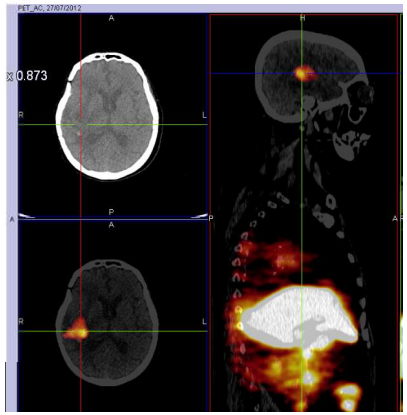
- Real theranostic potential
- Known and established production, quality control
- Produced by cyclotrons using Ni-64 or Zn-68
- High specific activity production (n.c.a.)
- Positron, beta and Auger emission
- Existing experience in the Member States







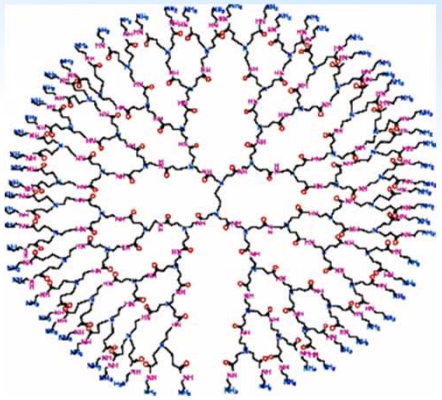




- The Quarterly Journal of Nuclear Medicine and Molecular Imaging 2020 December;64(4):338-45

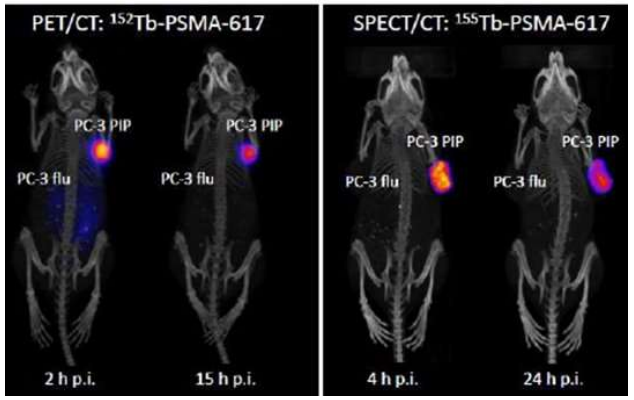
Planned CRP: Novel delivery systems for radiopharmaceuticals: formulation and preclinical evaluations; 2025

- To implement and supervise the CRP on Novel delivery systems for radiopharmaceuticals: formulation and preclinical evaluations, to reduce the existing side effects as well as improving the quality and effects of existing radiopharmaceuticals. The CRP will look into development of drug delivery systems to elongate the biological half lives, pharmacokinetics and decreasing the side effects.

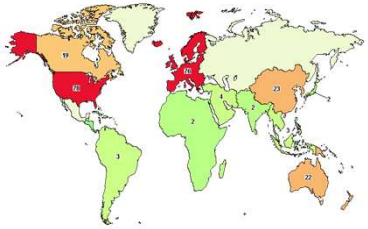


Planned CRP: Production and quality control of Terbium theranostic radiopharmaceuticals; 2026

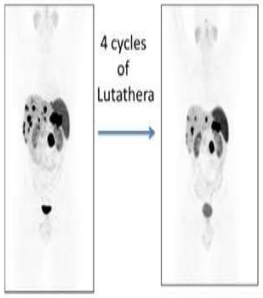
- Terbium offers 4 clinically interesting radioisotopes with complementary physical decay characteristics: (149)Tb, (152)Tb, (155)Tb, and (161)Tb.
- The preparation of radiopharmaceuticals with identical pharmacokinetics useful for PET ((152)Tb) and SPECT diagnosis ((155)Tb) and for α- ((149)Tb) and β(-)-particle ((161)Tb) therapy.



Recent developments in Lu-177 radiopharmaceuticals



- Currently there are over 70 radiopharmaceuticals for therapy in clinical trials and about 50% of them are based on ^{177}Lu alone
- The mainstream includes radiopharmaceuticals for NETs and Prostate Cancer



Lutathera: 2018

Two Lu-177 based drugs approved for radionuclide therapy

Lutathera for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours in adults.

FDA approves Lu-177 PSMA-617 for prostate cancer treatment

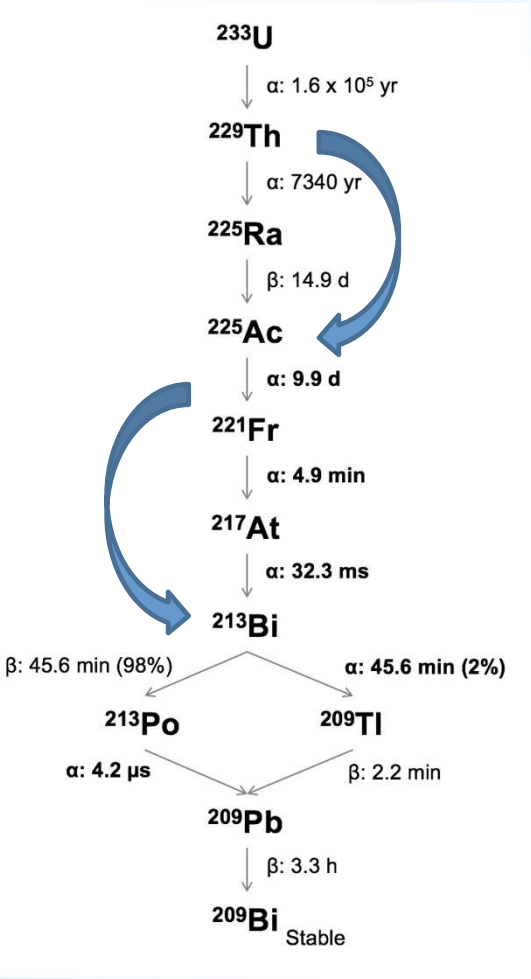
By Will Morton, AuntMinnie.com staff writer

March 23, 2022 -- The U.S. Food and Drug Administration (FDA) has approved lutetium-177 (Lu-177) prostate-specific membrane antigen radioligand therapy (Pluvicto, Novartis) for the treatment of patients with metastatic prostate cancer.

Different Enzyme inhibitors, peptides and other tumour microenvironment specific ligands are under evaluation in nonclinical and clinical studies

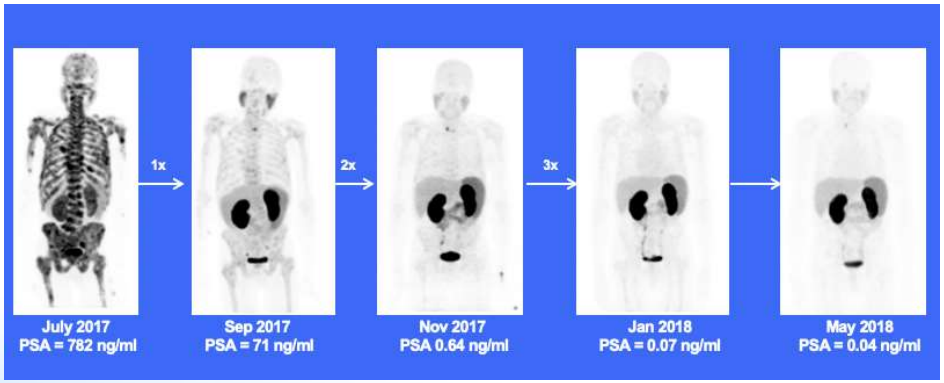
Extra budgetary funds are needed to accommodate large number of proposal (40) received

Ac-225



Decay scheme of ^{225}Ac

- **Radiochemical extraction** of Actinium-225 (T1/2= 9,9 d) from Thorium-229 (T1/2= 7317 y) sources.
- **Cyclotron:** Irradiation of Radium-226 with medium energy protons (16 MeV): **Ra-226 (p,2n) Ac-225.**
- **Cyclotron:** Irradiation of Thorium-232 with high energy protons:**Th-232 (p,x) Ac-225/Ac-227.**
- **Research Reactor:** Irradiation of Radium-226 for production of Th-229: **Ra-226 (3n,γ)Ra-229 → Ac-229 → Th-229.**
- **Linear Accelerator:** Irradiation of Radium-226 with high energy protons and photonuclear transmutation : **Ra-226 (γ,n) Ra-225 →Ac-225.**



Mike Sathekge et al, European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:129–138

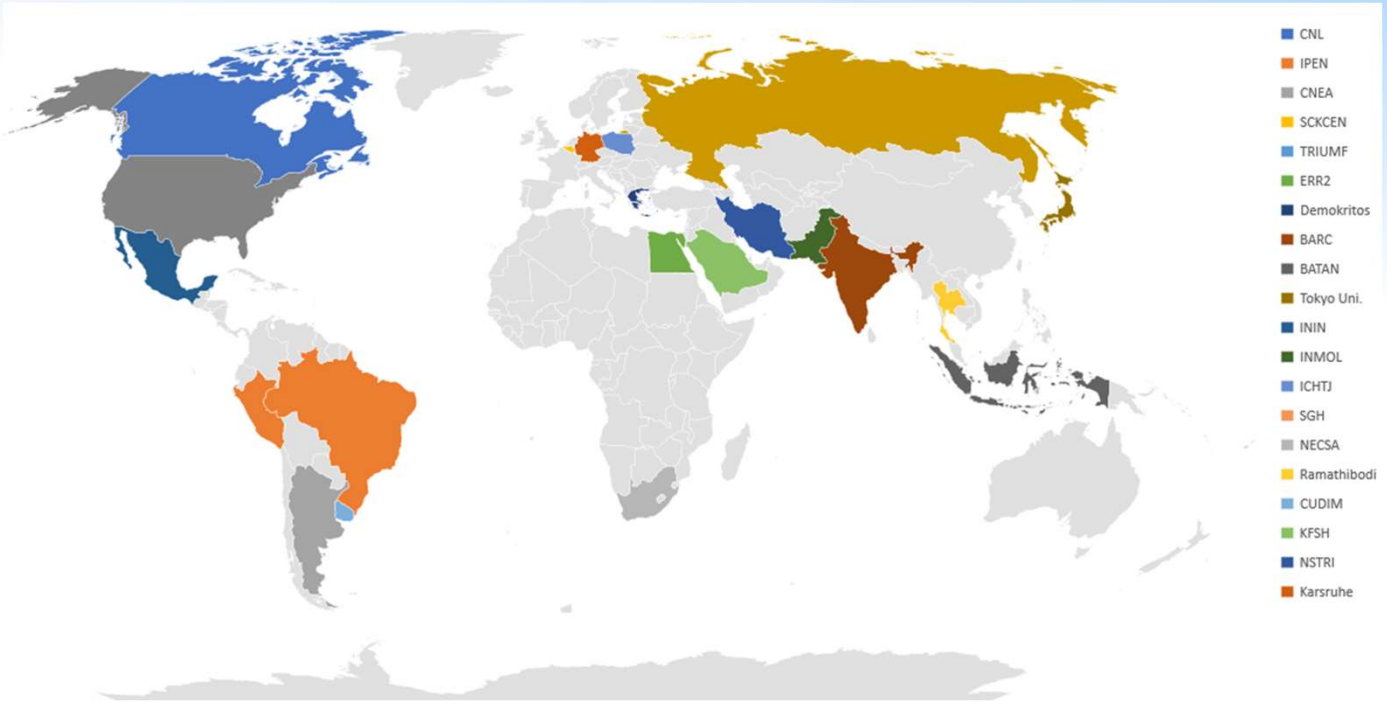
F22075: Production and Quality Control of Ac-225 Radiopharmaceuticals

Planned duration:

- 2022-2026 (5 years)
- Budget: Regular Budget (RB)+External Budget from Industry
- 52 proposals received
- 25 approved

1st RCM in Nov. 2022
2nd RCM July 2024

Ac-225 samples provided for MSs:
Japan, Uruguay, Greece, Mexico, Brazil, etc.

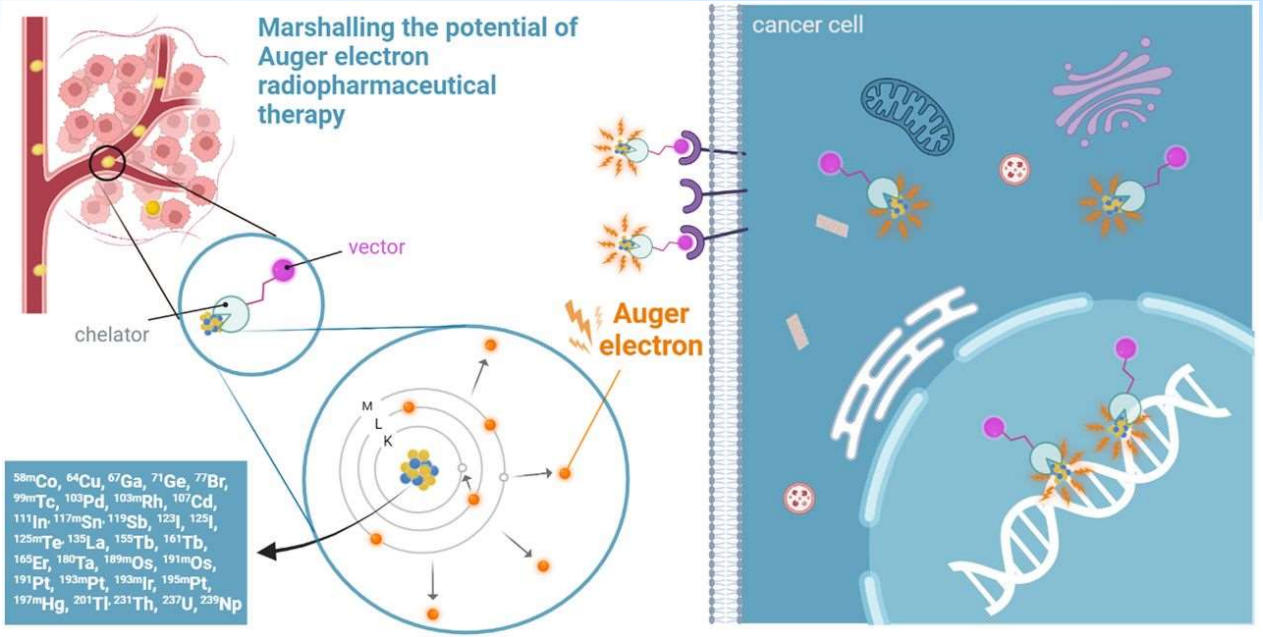


New alpha emitters

- New alpha emitters present various challenges which must be overcome before they can be used routinely in the clinical. E.g.,
- Short half-lives of some alpha emitters (At-211, Pb-212, Tb-149) may preclude them from a centralized distribution network. This would require regionally placed particle accelerators or radionuclide generators in several geographic locations to support their clinical use.
- Recoil effects can cause progeny to become unbound and travel from the targeted site. Dosimetry will determine the significance of this phenomenon.
- Each has its own production challenges.

Radionuclide	Emission	Half-life (hrs)	Production Mechanism
^{211}At	α	7.2	^{210}Bi(α,2n)
^{225}Ac	α (5.8 MeV) β (0.1 MeV)	240	^{229}Thorium generator Generator production from ^{225}Ra ^{226}Ra(p,2n), or ^{226}Ra(γ,p)
^{224}Ra/ ^{212}Pb/ ^{212}Bi	α (5.7 MeV)/ β^- (0.1 MeV)/ α (6.0 MeV), *β* (0.77 MeV)	3.7/ 10.64 h /60 .6 m	^{226}Ra(*γ*,2n)
^{165}Er	A (0.038 MeV) γ (0.05 MeV)	10.3	^{166}Er(γ,n)
^{149}Tb	α (3.967 MeV) β (0.7MeV)	4.12	^{152}Gd(p,4n)^{149}Tb, Ta(p, X)^{149}Tb

Technical Meeting on *Auger Electron-Emitters for Radiopharmaceutical Developments,* September 2022.



FOCUS ON MOLECULAR IMAGING

Marshalling the Potential of Auger Electron Radiopharmaceutical Therapy

Julie Bolcaen[1], Mohamed A. Gizawy[2], Samantha Y.A. Terry[3], António Paulo[4], Bart Cornelissen[5], Aruna Korde[6], Jonathan Engle[7], Valery Radchenko[8,9], and Roger W. Howell[10]

DOI: https://doi.org/10.2967/jnumed.122.265039

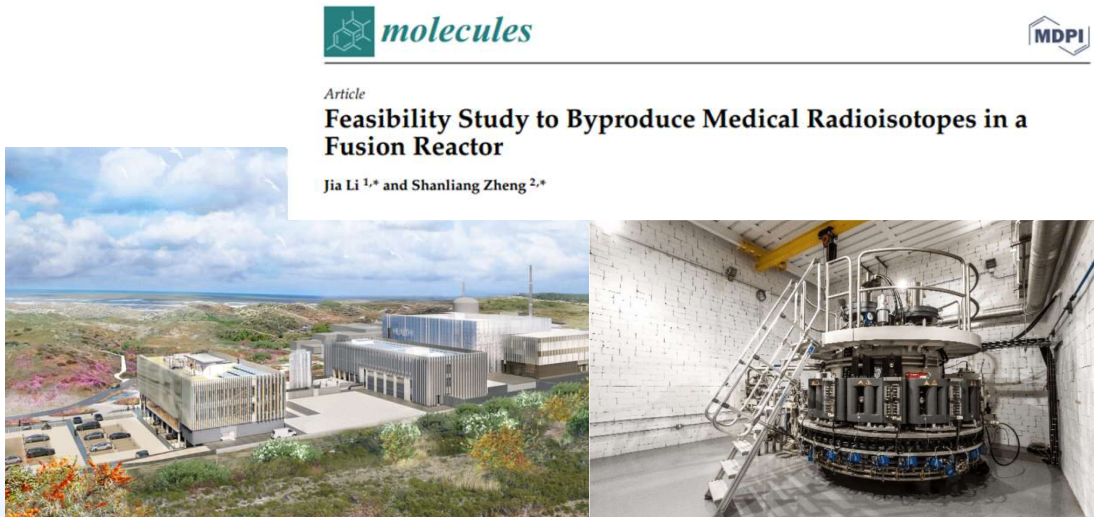
Radiopharmaceuticals are big business

- Over 150 companies are currently actively developing radiodiagnostic or radiotherapeutic pharmaceuticals
- The radiopharmaceutical market is expected to double by the year 2030 (USD 5.5 billion in 2022)
- Venture capital investments in the area have more than quadruple in the past 6 years.

Radiopharmaceuticals are big business but patients needing them are vulnerable and access is not equitable across the globe.
Goal: leave no one behind.

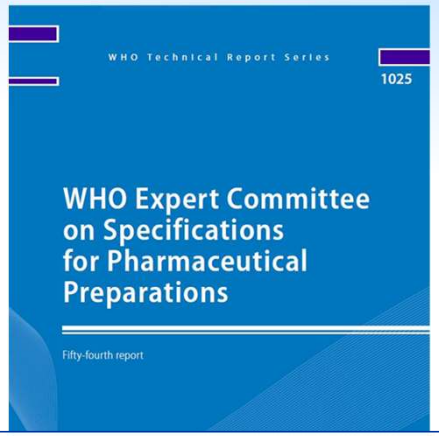
Drivers:

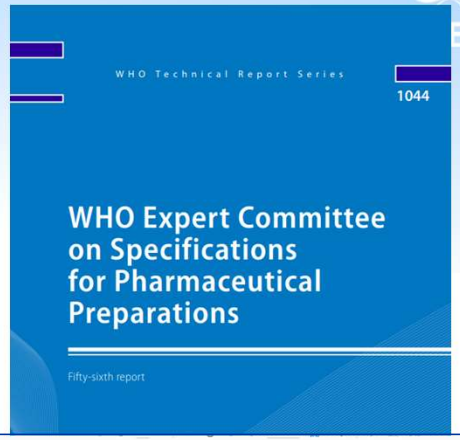
- ***Personalised medicine and increasing cancer rates***
- ***Success of existing & new products***
- ***Variety in radioisotope production:***
  - *Photodynamic route (Mo-98, Cu-67, Ac-225, etc.; Shine, PanTera, etc.)*
  - *Application of nuclear power reactors in radioisotope production*
  - *Fusion based radioisotope production (neutron sources)*
  - *A means for using nuclear waste stockpiles (e.g. Ra-226, U-233)*



IAEA/ WHO GMP Guidelines for Radiopharmaceuticals

- Good manufacturing practices (GMP) for radiopharmaceutical products are a set of practices, using a traceable process, that ensure that radiopharmaceutical products are consistently produced and controlled to the quality standards appropriate for their intended use, and designed to consistently yield the radiopharmaceutical product.
- GMP fall under the umbrella of the overall quality management system (QMS)
- IAEA in collaboration with WHO published the GMP guidelines for radiopharmaceutical products.
- Use of investigational radiopharmaceuticals is increasing, hence specific guidance on investigational GMP was published in 2022
- Cold kits for radiopharmaceutical preparation can be produced in-house on small scale, the GMP guidance for this is in process.





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).

These guidelines were updated by the following experts (in alphabetical order): Ms Y.M. Chevalme (France), Dr S. Kopp (WHO, Switzerland), Ms A. Korde (IAEA, Austria), Mr S.K. Lyashchenko (United States of America), Mr J.A. Osso Junior (IAEA, Austria), Mr A. Ross (Canada) and Mr S. Todde (Italy).

Annex 3

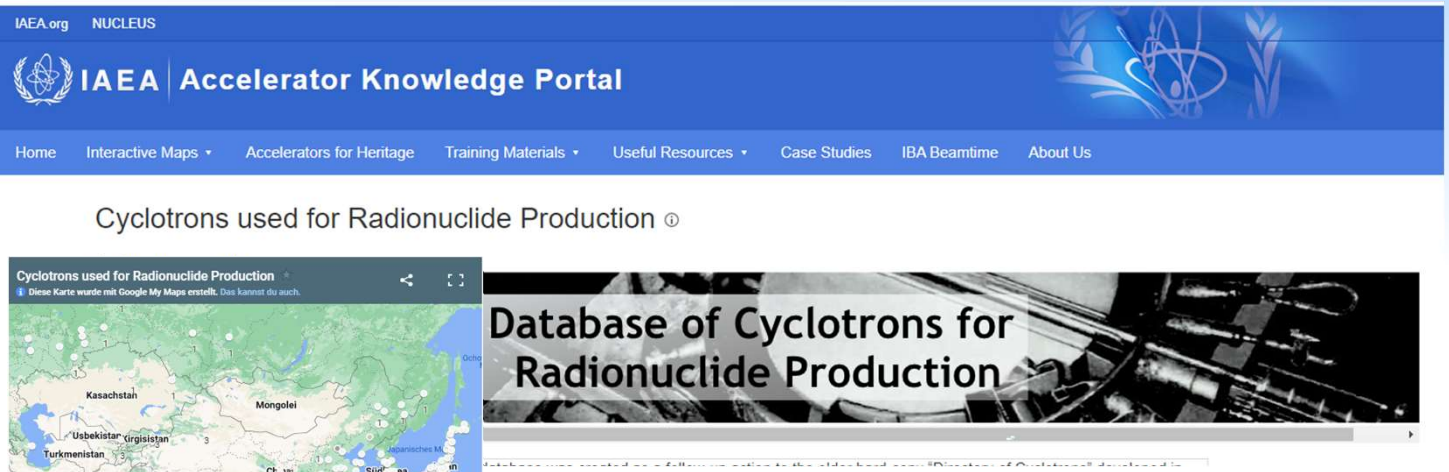
IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products

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



Database: Cyclotrons used for Radionuclide Production

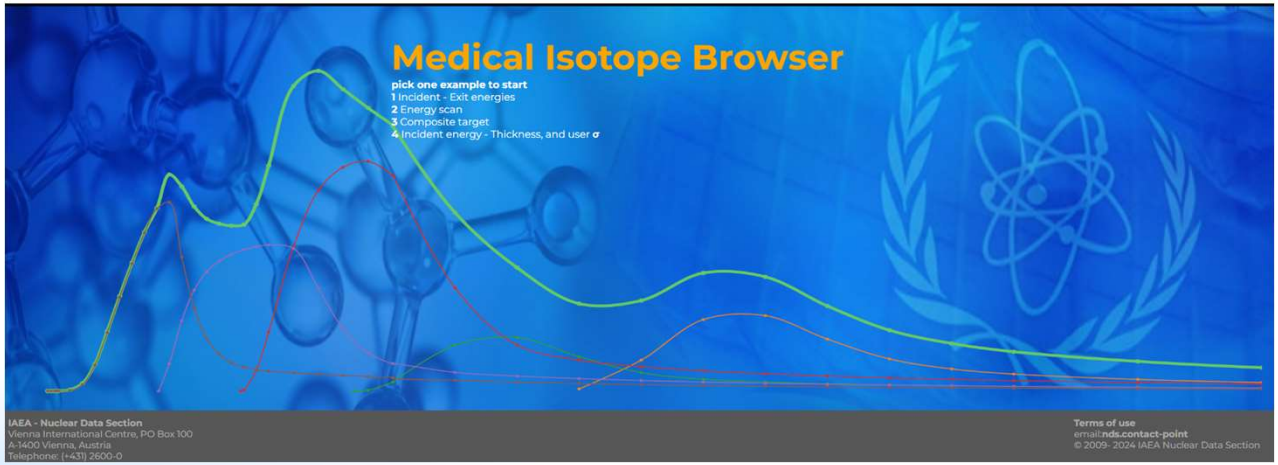
https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx

>1350 cyclotrons 89 MSs

IAEA Medical Isotope Browser:

https://www-nds.iaea.org/relnsd/isotopia/isotopia.html

A predictive tool for medical radioisotope production



International Symposium on Trends in Radiopharmaceuticals

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Price: €38.00

2016

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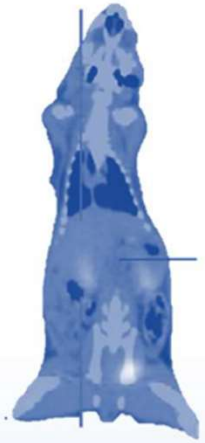
IAEA Radioisotopes and Radiopharmaceuticals Reports 1

Upcoming Webinar

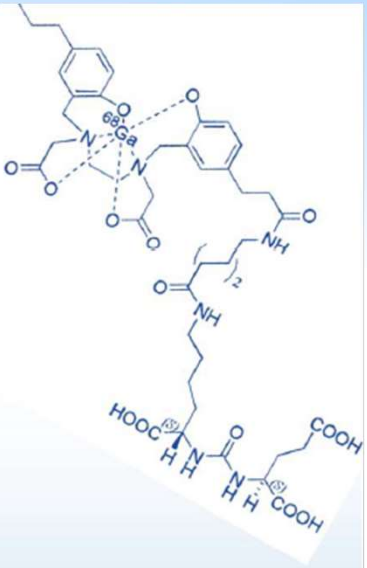


Please join the IAEA webinar on:

Production and Quality Control of Cyclotron Based Ga-68 Radiopharmaceuticals

Wednesday, 29th May 2024

14:00 –16:00 CET



Opening

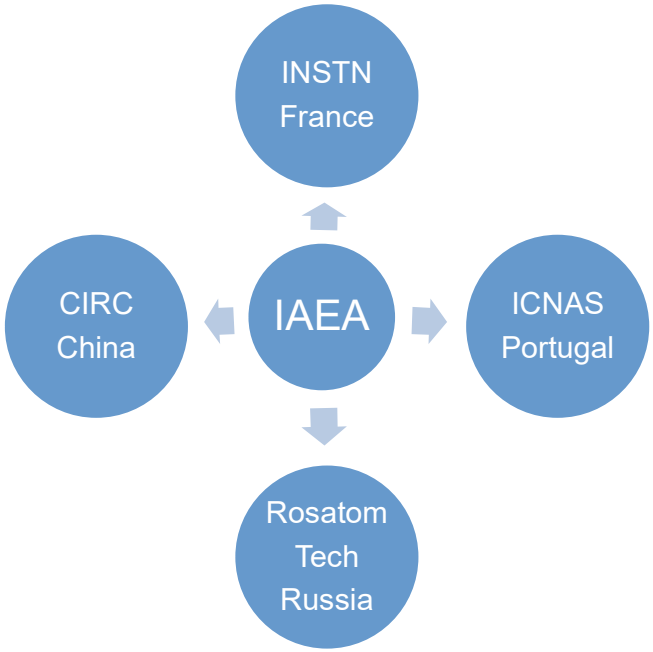
Ms. Melissa Denecke, Director, Division of Physical and Chemical Sciences, IAEA
Ms. Celina Horak, Section Head, RCRT, IAEA
Mr. Amir Jalilian, Scientific Secretary, RCRT, IAEA

Speakers

Mr. David Dick, USA
Mr. Miguel Avila-Rodriguez, Mexico
Ms. Robin Ippisch, USA
Ms. Brigitte Guérin, Canada
Ms. Katie Gagnon, Sweden
Ms. Cristiana Gameiro, Belgium
Mr. Antero Abrunhosa, Portugal
Ms. Ellen Pel, France

Register Here.

IAEA - Collaborating Centres in Radiopharmaceuticals



Practical Arrangements with professional societies : SRS, EANM

Recent activities with collaborating centre

ICNAS PRORTUGAL

- TM on Preclinical studies 2021
- TM on production of RI using cyclotron 2022
- Support for ISTR2023 : Speakers, exhibition
- Support for EM>10, FS>50 (2021-23)

INSTN FRANCE

- Summer school on radiopharmaceuticals from fundamentals to the applications 12-23 June 2023
- For French speaking African country participants

CIRC CHINA

- Technical workshop on therapeutic radioisotopes & radiopharmaceuticals, August 2023.
- Asia Pacific region participants

IAEA
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Thank you!