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REVIEW ARTICLE

IAEA Activities on ^{67}Cu, ^{186}Re, ^{47}Sc Theranostic Radionuclides and Radiopharmaceuticals

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Abstract: Despite interesting properties, the use of ^{67}Cu, ^{186}Re and ^{47}Sc theranostic radionuclides in preclinical studies and clinical trials is curtailed by their limited availability due to a lack of widely established production methods. An IAEA Coordinated Research Project (CRP) was initiated to identify important technical issues related to the production and quality control of these emerging radionuclides and related radiopharmaceuticals, based on the request from IAEA Member States. The international team worked on targetry, separation, quality control and radiopharmaceutical aspects of the radionuclides obtained from research reactors and cyclotrons leading to preparation of a standard recommendations for all Member States. The CRP was initiated in 2016 with fourteen participants from thirteen Member States from four continents. Extraordinary results on the production, quality control and preclinical evaluation of selected radionuclides were reported in this project that was finalized in 2020. The outcomes, outputs and results of this project achieved by participating Member States are described in this minireview.

Keywords: ^{67}Cu, ^{186}Re, ^{47}Sc, IAEA, CRP, theranostic, research reactor, cyclotron.

1. INTRODUCTION

The past decade has been met with a significant growth in ^{68}Ga and ^{177}Lu-radiopharmaceuticals playing an effective role as an almost perfect theranostic pair. This is attributed in part to the availability of commercial generators which gave rise to a chemically useful [^{68}Ga]$GaCl_3$. As such, ^{68}Ga is the first widely accessible radiometal for PET, and is nicely matched with the available [^{177}Lu]$LuCl_3$ from research reactors through direct and indirect routes. However, despite the growth in the use of ^{68}Ga and ^{177}Lu, the quest for additional radionuclides for theranostic applications continue for many reasons including:

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- a longer-lived PET radionuclide to facilitate logistics of distribution or allowing imaging out to longer time points
- a higher energy β^- emitter
- a shorter half-life β^- emitter
- a matched pair (*i.e.* an imaging and therapy nuclide of the same element)

Among the several theranostic concepts, the most recent approach includes the use of a single radionuclide, emitting both a therapeutic radiation and a low-energy gamma ray which could be used for dosimetric evaluation *via* SPECT process, and some of the notable radionuclides belonging to this category are ^{67}Cu, ^{186}Re, and ^{47}Sc. However, their use in preclinical and clinical trials is curtailed by their limited availability due to a lack of widely established production methods. Based on requests from IAEA Member States on the development and support on production and application of radionuclides and radiopharmaceuticals, an IAEA Coordinated Research Project (CRP) entitled *" Therapeutic Radiopharmaceuticals Labelled with New Emerging Radionuclides (^{67}Cu, ^{186}Re, ^{47}Sc" F22053)* [1], was initiated in 2016 to address the need to explore the most promising methods to produce the remaining three nuclides. These nuclides were selected based on their theranostic properties (see Table **1**), their dual production routes through reactors and cyclotrons, target availability, the potential for high specific activity production, and, in the case of ^{67}Cu and ^{47}Sc, having also matched-pair PET nuclides (*e.g.* ^{60,61,64}Cu and ^{43,44}Sc) [2].

If one reviews clinical trial data on "clinicaltrials.gov" website for use of different radioisotopes of these three nuclides, a growing trend in the past decade can be observed. Most of such studies were diagnostic in nature, including two very recent trials with ^{67}Cu, and five clinical trials with ^{186}Re [3] (Fig. **1**).

2. THE CRP STORY

To stimulate progress in medical applications of radionuclides, IAEA organized a Consultants' Meeting with the title of "*Preparation of CRP on Therapeutic Radiopharmaceuticals Labelled with New Emerging Radionuclides"* in October 2014. Several experts from Member States discussed the important gaps in the theranostic radiopharmaceutical developments, especially the need for new theranostic radionuclides that would have extraordinary chemical, and physical properties. Among the selected radionuclides were ^{64}Cu, ^{47}Sc, ^{67}Cu, and ^{186}Re, with rather long half-lives, photon and soft beta emission, and well-known chelation chemistry. Due to robustness and available expertise on ^{64}Cu, a separate CRP was initiated on ^{64}Cu-theranostic radiopharmaceuticals.

During 2016-2020, the CRP explored the most promising methods to produce the remaining three radionuclides. The investigated nuclear reactions were largely dependent on the different types of available facilities (*e.g.* reactor/accelerator) and corresponding particle availability, energy ranges, nuclear data, targetry, irradiation, purification, quality control, and in some cases radiopharmaceutical aspects. Fig. **2** highlights the main topics investigated during this CRP.

^{47}Sc, ^{67}Cu, and ^{186}Re can be produced using research reactors and according to the IAEA research reactor portal [4], about 70 such facilities are currently operating worldwide. On the other hand, these radionuclides can also be produced with particle accelerators, including high energy proton linacs, electron linacs, or/and a broad network of cyclotrons as demonstrated in the IAEA database; *Cyclotrons used for Radionuclide Production* [5]. Therefore, significant production potential exists for most of the Member States for these radionuclides. Twenty-nine proposals to participate in the CRP were received from 13 Member States and 14 such proposals were selected (two from Poland) (Table **2**) based on the quality of the proposal, available infrastructure and human resources, and thought-through workplan.

(Fig. **3**) shows the worldwide distribution of Member States working in this CRP. The participants enabled highly collaborative efforts leveraged by the unique expertise offered by each of the groups. For example, CRP participants from Egypt, India, Iran, and Poland had significant experience with nuclide production with reactors; CRP participants from France, Hungary, Iran, Italy, and Malaysia had expertise related to cross section measurements and/or theoretical modelling of production yields; CRP participants from Republic of Korea, Iran, Poland, Syria, and USA were experienced in target preparation (including its recycling); CRP participants from Egypt, France, Japan, India, Iran, Italy, Syria, Poland, and USA were experts in isotope purification techniques; and finally CRP participants from Egypt, India, Poland, Saudi Arabia, and USA had experience in peptide chemistry and radiolabelling.

This article is not a full review on the worldwide situation of the radionuclide production, rather it focuses on the work done by the CRP participants. For simplicity, this minireview presents a summary for each radionuclide in subsections of Nuclear Data, Target Preparation, Purification, Quality Control and Radiopharmaceutical Production.

3. METHODS

3.1. Copper-67

3.1.1. Nuclear Data

The production of no-carrier added ^{67}Cu by using nuclear reactors is feasible *via* the ^{67}Zn(n,p)^{67}Cu reaction using fast neutron fluxes (> 1 MeV) and was investigated in this CRP. The ^{66}Cu(n,γ)^{67}Cu nuclear reaction is not considered favourable due to the low production yield of ^{67}Cu in carried-added form [6]. The ^{68}Zn(n,d) reaction is also not considered favourable due to low yields.

Accelerator-based production of ^{67}Cu has been investigated thoroughly over the last years with various reactions considered using Ni, Zn and Ga targets. The most common methods include ^{68}Zn(p,2p)^{67}Cu, ^{68}Zn(n,np)^{67}Cu, and

^{68}Zn(γ,p)^{67}Cu. During the CRP the production methods were evaluated, and the most promising reactions were selected based on the production yield, the co-production of contaminant radionuclides (in particular ^{64}Cu, with a half life of 12.701 hours), and the economic feasibility [7-9]. Reactions on nickel targets are also possible, such as ^{64}Ni(α,p)^{67}Cu using alpha particle accelerators.

3.2. Target Preparation

For accelerator-based production, several possible methods to prepare targets have been established, which may be adjustable and affordable to each target system/infrastructure. Various processes are well established and practical for cyclotron targets, such as electroplated enriched Zn target on

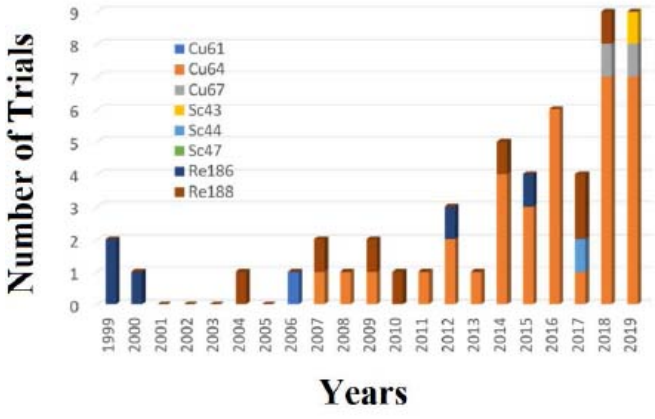

Fig. (1). Clinical trials starting by year as tabulated from clinicaltrials.gov for medically relevant Cu, Re, and Sc isotopes (accessed Nov. 2019). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

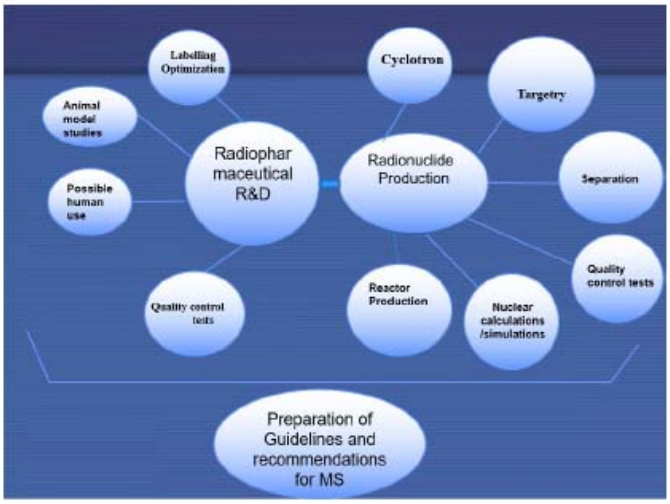

Fig. (2). Schematic view of the items covered during the CRP on the theranostic radionuclides. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Physical characteristics of the CRP theranostic radionuclides.

Radionuclide	Half-Life	β$^-$ emission	β$^-$ mean energy	Dominant γ emission	Candidate PET nuclide(s)
^{67}Cu	2.58 d	100%	141 keV	185 keV (48.7%)	^{60}Cu, ^{61}Cu, ^{64}Cu
^{186}Re	3.72 d	92.53%	346.7 keV	137 keV (9.4%)	Not suitable
^{47}Sc	3.35 d	100%	162.0 keV	159 keV (68.3%)	^{43}Sc, ^{44}Sc

Table 2. List of institutes participating in the CRP.

Institutes	Member State	Radionuclide(s)	Methods
Egyptian Atomic Energy Authority	Egypt	^{47}Sc	Research reactor
GIP ARRONAX	France	^{67}Cu	Cyclotron
Institute for Nuclear Research	Hungary	^{186}Re, ^{47}Sc, ^{67}Cu	Nuclear calculations for cyclotrons
Bhabha Atomic Research Centre	India	^{186}Re, ^{47}Sc, ^{67}Cu	Research reactor, Cyclotron
Nuclear Science and Technology Research institute	Iran	^{67}Cu,^{47}Sc	Research reactor, Cyclotron
Istituto Nazionale di Fisica Nucleare (INFN)	Italy	^{67}Cu,^{47}Sc	Cyclotron
National Institutes for Quantum and Radiological Science and Technology	Japan	^{186}Re,^{67}Cu, ^{47}Sc	Cyclotron
Korea Atomic Energy Research Institute	Korea (Republic of)	^{67}Cu	Cyclotron
University of Malaya	Malaysia	^{186}Re	Cyclotron
National Centre for Nuclear Research & Institute of Nuclear Chemistry and Technology	Poland	^{67}Cu, ^{47}Sc	Research reactor, Cyclotron
King Faisal Specialist Hospital and Research Centre	Saudi Arabia	^{67}Cu	Cyclotron
Atomic Energy Commission of Syria (AECS)	Syria	^{67}Cu, ^{186}Re	Cyclotron
University of Alabama at Birmingham	USA	^{47}Sc	Cyclotron

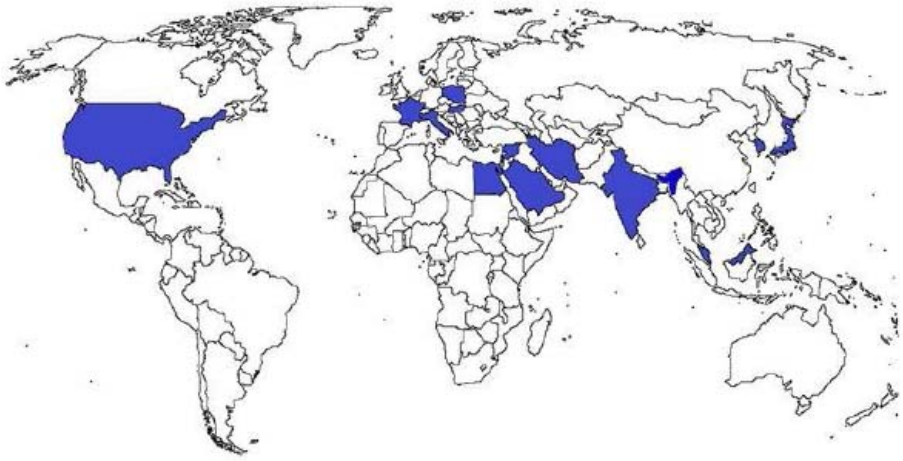

Fig. (3). Worldwide distribution of Member States (in blue shades) working in this CRP. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

a gold electroplated layer optimized for the specific beam energy [10]. For facilities already using ^{64}Ni targets for ^{64}Cu and with access to alpha beams, it is possible to divert the entire remote production system for ^{67}Cu [11].

To prepare a target for the reactor-based production method, usually an appropriate amount of zinc oxide powder (natural with 4.1% or ^{67}Zn) is encapsulated in quartz ampule and then placed in an aluminium irradiation container. After performing initial quality tests, the prepared target is irradiated in nuclear reactor with fast neutrons.

3.3. Purification

^{67}Cu extraction from the irradiated Zn target requires column chromatography, typically with anion exchange resins. This process is well-known, however, if large amounts of Zn need to be processed, the use of ion exchange methods may demonstrate poor results, presumably due to overloading of ionic species. To overcome this challenge, the Japanese group investigated a co-precipitation method using H_2S and Ag^+ as an alternative way to isolate ^{67}Cu from a bulky amount of ^{68}Zn and other metallic impurities. In contrast, when separating ^{67}Cu prepared from an electroplated ^{64}Ni target a well-known procedure was used as described in another IAEA CRP [12] and publications [13]. Polish group conducted studies on the potential use of solid phase extraction chromatography for Cu using a Triskem resin. The Indian group used liquid-liquid extraction technique using dithizone as the extractant to separate ^{67}Cu from the neutron irradiated zinc oxide target.

3.4. Quality Control

The Chemical purity of the final product was determined using ICP-MS methods with very high sensitivity. However,

a quick HPLC post-column method based on ion-chromatography was also introduced (*e.g.,* Fe^{3+}, Cu^{2+}, Ni^{2+}, Co^{2+}, and Mn^{2+}) by the Japanese team [14]. The chemical purity of [^{67}Cu]$CuCl_2$ was also determined by anodic stripping voltammetry for zinc and copper impurities. To confirm the radionuclidic purity and check the potential impurities of ^{64}Cu and ^{65}Zn, gamma spectroscopy methods using HPGe detectors were applied. Radiochemical purity was checked using recent published methods.

3.5. Target Recovery

Zinc recycling is a well-known process and used routinely for ^{67}Ga production, as reported in IAEA Tec-Doc No. 468 published in 2009 [15]. The process uses adsorption of anionic complexes of metal ions including enriched zinc on a strong acidic cation resin (Dowex 1-X8 (100-200 mesh, Cl- form), elution of other unwanted metals in anionic form, and finally the elution of Zn. For ^{64}Ni recovery, a method reported in IAEA Tec-Doc No. 432 published in 2004 [16] can be applied. Alternatively, ^{64}Ni can be recovered from the target dissolved in hydrochloric acid aqueous solution and treated using solvent extraction and cation exchange resin column chromatography [17].

3.6. Radiopharmaceutical Production

Several DOTA-based peptide radiopharmaceuticals were studied during the CRP by groups from Japan (RGD), Saudi Arabia and Syria (DOTATOC) which the data is under publication. Corresponding protocols for radiolabelling, quality control, and preclinical studies were developed. Two pre - clinical studies were carried out with ^{67}Cu-labelled compounds in Japan [18, 11].

4. RHENIUM-186

4.1. Nuclear Data

Rhenium-186 is an interesting radionuclide, with chemistry which is in many ways similar to ^{99m}Tc, however with both imaging and therapeutic capabilities the in case of ^{186}Re [19]. It can be produced in a research reactor using neutron capture on an enriched ^{185}Re target (37.4% natural abundance) with a large cross-section (~112 b) [20]. Alternatively, it can be produced *via* neutron activation ^{187}Re(n,2n)^{186}Re (62.6% natural abundance) with ~2b cross section [21]. However, the resulting ^{186}Re is carrier added and thus cannot be used for high specific activity radiopharmaceuticals such as peptides. Several small molecule radiopharmaceuticals which do not require high specific activity and can be manufactured using carrier-added ^{186}Re (*e.g.,* bone pain palliation agents). Although yields are lower than reactor-based reactions, production of ^{186}Re with accelerators (cyclotrons or spallation machines) can result in high specific activity no - carrier-added ^{186}Re suitable for targeted radiopharmaceutical therapy although the yields are lower. The Malaysian team evaluated the production cross-sections for ^{186}Re *via* charged particle induced reactions on W [22, 23] and identified the ^{186}W(d,2n)^{186}Re reaction as the cleanest production route.

4.2. Target Preparation

To produce ^{186}Re in research reactors, *via* the ^{185}Re(n,γ)^{186}Re reaction, enriched ^{185}Re in form of oxide is typically used similarly to other reactors-based metallic radionuclides already covered in IAEA Tec-Doc No. 1340 [6]. For accelerator-based production, elemental W powder or pressed powder in the form of WO_3 form is used with Cu backings. Target recovery can be performed with ion-chromatography and electrolysis. The French group used the ^{186}W(d,2n)^{186}Re reaction with deuteron energies from 3.6 to 16.6 MeV using tungsten oxide targets [24]. The Indian team, on the other hand, used WO_3 powder pressed this into a grooved aluminium holder to form a pellet. The Japanese team used the ^{186}W powder in a ceramic (SiC) target box. The Syrian team used the ^{186}W(p,n)^{186}Re reaction with an electroplated target fixed on a copper target holder.

4.3. Purification

The Indian team used the dissolved target for selective electrodeposition of ^{186}Re radionuclide from the radioactive solution [25]. At the same time, other teams used cartridge-based methods. For instance, the Japanese group used two chelating resins, while the Syrian team loaded the irradiated tungsten target solution on the preconditioned TEVA cartridge followed by formulation in normal saline for injection.

4.4. Quality Control

Two CRP teams (India and Syria) suggested and developed a method for chemical purity determination using ICP-AES analyses after one-month cooling time for Tungsten impurity detection [25]. For radionuclidic purity, the team performed gamma ray spectroscopy analysis one hour after end of processing. To test radiochemical purity, an ITLC method was suggested and successfully applied by some participants, including Japanese team.

4.5. Radiopharmaceutical Production

The most commonly used chelating agents for attaching ^{186}Re to biomolecules are N_2S_2, *e.g.* EC, and N_3S donor types ligands, such as MAG_3 [26]. The Syrian team performed preparation, quality control, and evaluation of ^{186}Re-MDP, ^{186}Re-HEDP. The Indian team performed ^{186}Re-DMSA and ^{186}Re-HEDP preparation and quality control.

5. SCANDIUM-47

5.1. Nuclear Data

Scandium-47 can be produced in a nuclear reactor and the Indian, the Egyptian, and the Polish teams investigated this method, specifically ^{46}Ca(n,γ)^{47}Ca→^{47}Sc reaction (cross section is 0.74 b, ^{46}Ca natural abundance is 0.004%). Hence, to obtain significant activity of ^{47}Ca, target enriched in ^{46}Ca must be used by the above-mentioned reaction, which is very expensive. Previously Polish group studied the neutron

irradiation of Ti targets [27]. This method was also investigated by the Egyptian team using MCNPX code to estimate the levels of radionuclides produced during as well as post irradiation and the computational results were compared with experimental measurements.

The CRP teams also studied accelerator-based production of ^{47}Sc working with Ca, Ti, and V targets and compared the results. ^{47}Sc can be also produced indirectly by beta decay of ^{47}Ca. This process requires double chemical separation: first right after the end of irradiation (*e.g.* 3h), to remove all the Sc isotopes produced during irradiation, and second, after a few days of decay (*e.g.* ~ 134 h) to extract ^{47}Sc and stable ^{45}Sc.

5.2. Target Preparation

For cyclotron target preparation, both CaO and elemental Ca were used. Due to established chemical handling, various Ca targets (pressed, electro-deposited, *etc.*) are available for irradiation at the respective target stations including drawer targets, powder caps, *etc* [28]. The Japanese team evaluated the production feasibility of ^{47}Sc with ^{44}CaO target activated by alpha particles. The Iranian team used Ti targets in the form of ^{nat}Ti foil or by pressing the $^{nat}TiO_2$ powder into a pellet which was placed into an aluminium canister [29, 30]. The Italian team reported production of ^{47}Sc with natural vanadium targets [31]. The US team developed targets made both of titanium metal and titanium oxide powder (for further details, please read *"Accelerator Production of Scandium Radionuclides: Sc-43, Sc-44g, and Sc-47"* in this thematic issue). The Polish team investigated ^{47}Sc production by cyclotron irradiation of ^{48}Ca [32, 33]. The feasibility to produce high purity ^{47}Sc by neutron irradiation of ^{46}Ca targets in a nuclear reactor was investigated by the teams from Egypt [34], India, and Poland.

5.3. Purification

^{47}Sc purification from calcium targets performed by employing various methods including filtration of ^{47}Sc hydroxide, extraction from acidic chloride-based solutions with UTEVA resin extraction chromatography, and extraction chromatography with tripolyphosphate resin or N,N,N',N'-tetra-n-octyldiglycolamide resin were compared by Polish team [35]. The Egyptian team successfully reported separation of the reactor produced ^{47}Sc from natural calcium target using poly(acrylamide-acrylic acid)/multi-walled carbon nanotubes composite [36], as well as the separation of ^{47}Sc from neutron irradiated titanium target using a novel chitosan-acrylic acid/multiwalled carbon nanotubes composite. The US team developed techniques for the dissolution of Ti metal and oxide targets and a subsequent separation based on ion exchange chromatography with branched DGA resin, which was also performed by Italian and French groups.

5.4. Target Recovery

To recover the target for reactor-based production, the Indian team separated the enriched ^{46}Ca-amalgam from the aqueous electrolyte, while the Polish team recovered ^{46}Ca *via* precipitation of [^{46}Ca]$CaCO_3$. The US team developed Ti recycling based on a precipitation technique as well [35, 36].

5.5. Quality Control

For accelerator-based production, a protocol for detecting other radioscandium isotopes, in particular ^{46}Sc, was developed using γ-spectroscopy. For reactor-based production, the Indian and the Egyptian teams also used γ-ray spectrometry to verify that the levels of ^{47}Ca present in ^{47}Sc solution after the electrochemical separation step are permissible. To confirm the radiochemical purity, the Indian and the Egyptian groups developed ascending paper chromatography using two various mobile phase systems. For chemical purity, the Indian group determined the levels of mercury ions (as well as Fe, Cu, Mn, ion impurities) after electrochemical separation procedure, using cold vapour-graphite furnace atomic absorption spectroscopy (CV-GFAAS). The Polish group extensively studied the influence of metal ions on the Sc-labeling of DOTATATE, which can be quite useful for the production of related radiopharmaceuticals [37]. All teams determined sterility and bacterial endotoxins using well known pharmacopeia methods.

5.6. Radiopharmaceutical Production

It was suggested to evaluate the 'practical labelling activity' using a commonly used chelator, such as DOTA *esp.* DOTATATE [38], as reported by the Japanese, Polish and the US teams. All results proved to be of good quality and satisfactory for clinical applications that are under publication.

CONCLUSIONS AND RECOMMENDATIONS

Numerous routes have been investigated in this CRP for producing ^{67}Cu, ^{186}Re, and ^{47}Sc. This includes ^{67}Cu production from nickel or zinc targets, ^{186}Re production from tungsten targets, and ^{47}Sc from calcium, titanium, or vanadium targets. Also, for ^{47}Sc production, both the direct production route and the ^{47}Ca→^{47}Sc generator-like approach were studied. To choose the right method for each particular Member State, several parameters need to be considered, including the availability of particles (*e.g.* n, p, α, γ) of a suitable energy range, production yields, targetry, chemical separation methods, and radionuclidic impurities. In order to better choose the production route, it is helpful to refer to the IAEA Medical Isotope Browser tool [39].

Although the production of these radionuclides was addressed in this project, understanding the additional clinical radiation dose arising from the impurities is important and may involve dosimetry calculations and engaging with clinicians for input on acceptable specifications, *etc.* An additional consideration is the cost and the availability of the enriched target materials which may potentially be prohibitive. Regardless of which radionuclide a production site wishes to work with, and which production route is selected, for clinical production, it is important to establish quality control methods. IAEA has already prepared the guidelines for the

Member States which address quality control and assurance of emerging radiopharmaceuticals [40].

Photonuclear production of ^{67}Cu and ^{47}Sc was not specifically addressed in this CRP, however it is worthwhile mentioning that this method is very promising [41, 42] and IAEA has conducted activities regarding this field for possible initiation of a new CRP in the future.

Based on the results and experiments performed during this CRP in fourteen institutions worldwide, a new IAEA Technical Document is underway to provide recommendations on production, quality control and radiopharmaceutical production and labeling aspects of the ^{67}Cu, ^{186}Re, and ^{47}Sc theranostic radionuclides.

LIST OF ABBREVIATIONS

IAEA	=	International Atomic Energy Agency
CRP	=	Coordinated Research Project
PET	=	Positron Emission Tomography
ICP-MS	=	Inductively Coupled Plasma Mass Spectrometry
HPLC	=	High Performance Liquid Chromatography
HPGe	=	High Purity Germanium
Tec-Doc	=	Technical Document
DOTA	=	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)
DOTATOC	=	DOTA0-Phe1-Tyr3 octreotide
ICP-AES	=	Induced Coupled Plasma-Atomic Emission Spectroscopy
N2S2	=	Diamine-Dithiol
EC	=	Ethylene Dicysteine
N3S	=	Triamide-thiol
MAG3	=	Mercaptoacetyl-triglycine
MDP	=	Methylene Diphosphonate
HEDP	=	Hydroxy Ethylene Diphosphonate
DMSA	=	Dimercapto Succinic Acid
ITLC	=	Instant Thin Layer Chromatography
RTLC	=	Radio Thin Layer Chromatography
CV-GFAAS	=	Cold Vapour-Graphite Furnace Atomic Absorption Spectroscopy

CONSENT FOR PUBLICATION

We the authors of this manuscript, hereby, confirm and agree on the publication of this manuscript in the journal.

AVAILABILITY OF DATA AND MATERIALS

The data and materials in this paper can be available to all requesters according to the journal policy

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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