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Production and Quality Control of Actinium-225 Radiopharmaceuticals

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PRODUCTION AND QUALITY CONTROL OF ACTINIUM-225 RADIOPHARMACEUTICALS

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PRODUCTION AND QUALITY CONTROL OF ACTINIUM-225 RADIOPHARMACEUTICALS

INTERNATIONAL ATOMIC ENERGY AGENCY
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FOREWORD

Targeted alpha therapy is based on the application of alpha emitting radionuclides combined with selective delivery vectors (e.g. peptides, antibodies, nanoparticles). This is ideal from the perspective of the targeted radionuclide therapy concept, which enables maximum damage to targeted cells while minimizing toxicity to surrounding healthy tissues. Despite some promising clinical results, significant research is needed to optimize implementation of targeted alpha therapy. Questions remain involving aspects of microdosimetry, optimizing the formulation of targeted alpha therapy radiopharmaceuticals to enhance stability. To enhance comprehension of the therapeutic efficacy of an alpha emitter containing radiopharmaceuticals in clinical applications, an increased number of rigorously controlled studies are needed, thereby facilitating a more comprehensive understanding of their therapeutic potential. As such, this publication provides information on standardizing the production of these radiopharmaceuticals and making the results more accurate and translatable.

A major limitation of conducting extensive research on the most promising alpha emitters is the availability of alpha emitting radionuclides. A coordinated research project, entitled Production and Quality Control of Ac-225 Radiopharmaceuticals, was launched to foster the initiation of networks of radioisotope producers and radiopharmacy facilities to provide appropriate doses for patient application. The international need for development and circulation of standard procedures and guidelines for production, quality control and preclinical studies of alpha emitting radiopharmaceuticals, especially ^{225}Ac, was requested by IAEA Member States. The coordinated research project is expected to provide the latest state of the art in production and quality control techniques with application of ^{225}Ac based radiopharmaceuticals.

To address this need and in response to requests from Member States the coordinated research project was designed and supported by the IAEA from 2022 to 2026. This coordinated research project will focus on the production, quality control and preclinical evaluation of ^{225}Ac radiopharmaceuticals. This publication was compiled using input from experts in the field as well as preliminary results of the coordinated research project.

The IAEA wishes to thank the contributors involved in the preparation of this publication. The IAEA officer responsible for this publication was A. Jalilian of the Division of Physical and Chemical Sciences.

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CONTENTS

1. INTRODUCTION

1.1 BACKGROUND

Actinium-225 is an α emitting radionuclide that has garnered significant attention in the field of nuclear medicine for application in oncological treatments in Targeted Alpha Particle Radiotherapy (TAT). Alpha emitting radionuclides deliver highly localized and intense radiation to targeted cancer cells while minimizing damage to surrounding healthy tissues. This unique characteristic arises from the short range and high linear energy transfer of α particles, which allows for precise targeting and an increased therapeutic effect (Fig. 1) [1,2].

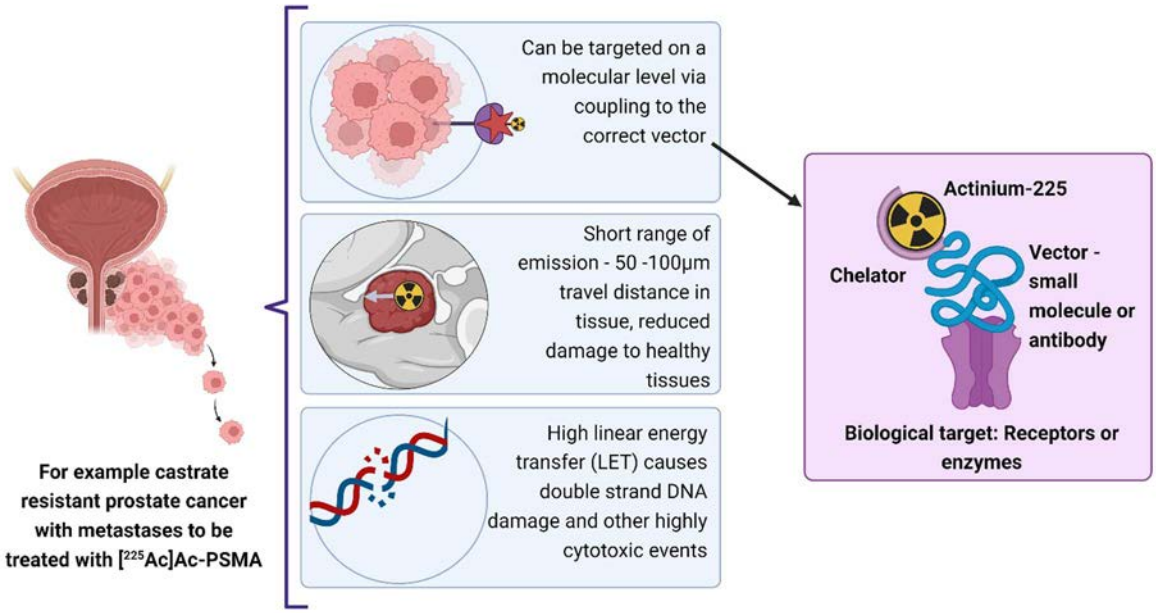

FIG. 1. Advantages of α emitting containing radiopharmaceuticals, for example [^{225}Ac]Ac Prostate Specific Membrane Antigen (PSMA), as therapeutic agents in oncology (courtesy of J. Kleynhans, KU Leuven).

The remarkable potential of ^{225}Ac radiopharmaceuticals in cancer treatment lies in its ability to selectively kill cancer cells by inducing double strand DNA breaks, a highly effective mechanism for inhibiting cell proliferation. The high linear energy transfer of α particles enables ^{225}Ac to deliver a significant amount of energy over a short distance, maximizing its impact on tumour cells. Research and clinical trials exploring the use of ^{225}Ac have demonstrated promise including the therapy of brain tumours, bladder cancer, neuroendocrine tumours, and leukaemia [3].

While ^{225}Ac holds great potential in the realm of targeted α particle therapy, ongoing research is focused on optimizing its production methods, refining dosimetry, and expanding its range of applications. As advancements continue, ^{225}Ac is an extremely attractive radionuclide in the evolving landscape of nuclear medicine, offering innovative solutions for the treatment of cancer and other challenging medical conditions [4,5].

The application of ^{225}Ac with its long half-life of 9.92 days and its higher cytotoxicity associated with the multiple alpha particles generated in its decay chain makes it very attractive. As of the writing of this document, based on a recent survey [6] it was reported that 27 molecules are currently in the development pipeline for ^{225}Ac based radiopharmaceuticals. Already, 13 of these compounds were reported to be administered in humans with one compound already in clinical phase III stage [6]. For more information on current clinical trials, refer to Section 2.4.

Since the production of sufficient ^{225}Ac to meet demand is the single most important factor in its widespread use, it is important to provide context on this issue. Zimmermann [6] provides a prediction on the future of ^{225}Ac production and this bodes well for the acceptance of this technology. It was calculated by Zimmerman that at 100 kBq/kg, a dose would require at least 10–12 MBq of ^{225}Ac as starting material. If each patient receives 3 doses, 3000 GBq of activity should be enough to treat 100 000 patients per year. According to Zimmerman, the global ^{225}Ac production capacity by 2032 is estimated to exceed 25 TBq, capable of generating at least 2 million patient doses annually. Recent years have witnessed significant investments in five different technologies for large scale production of ^{225}Ac. Companies are actively seeking solutions, exploring avenues such as securing access to domestic stocks or extracting radium from various sources, and Zimmerman predicts that the issue of demand should be resolved by 2025 [6]. The different methods of production of ^{225}Ac are discussed in Section 3.2. A prediction on how each of these methods will contribute to the supply of ^{225}Ac is provided by Radchenko and colleagues [4].

1.2 OBJECTIVE

The objective of this publication is to provide recommendations for safe handling and preparation of radiopharmaceuticals containing the α emitter ^{225}Ac with vectors targeting different types of tumour cells e.g., peptides (PSMA-617, PSMA-I&T, DOTA-Tyr3-Octreotate, DOTA-D-Phe1-Tyr3-Octreotide, DOTA-1-Nal3-Octreotide, etc.) or antibodies (J-591). The specific objectives for this publication as an outcome of the coordinated research project, include:

- A focus on the specifications of ^{225}Ac as received from various production sources and the implications on radiolabelling;
- Recommendations with regards to infrastructure and training requirements to produce ^{225}Ac based radiopharmaceuticals;
- Production of ^{225}Ac radiopharmaceuticals with the emphasis on small molecules and peptides;
- A discussion on the unique aspects of radiolabelling of antibodies with ^{225}Ac;
- In-depth guidance on the QC of ^{225}Ac based radiopharmaceuticals;
- Recommendations regarding radiation protection and waste management of ^{225}Ac.

1.3 SCOPE

This publication describes the recent advances in ^{225}Ac radiopharmaceutical production in brief, with a particular focus on practical aspects of radiolabelling, infrastructure requirements and the intricate QC processes that governs this radionuclide.

The publication is a result of the combination efforts of consultants who have state of the art expertise on the clinical production of ^{225}Ac radiopharmaceuticals. The experts find themselves at the forefront of academic research on ^{225}Ac and are aware of new developments as they happen. Whilst all production routes of ^{225}Ac are discussed with particular emphasis on the constraints, the chosen route will introduce to the radiolabelling of the ^{225}Ac radiopharmaceuticals, it is important to note that the bulk of the knowledge gained on ^{225}Ac radiopharmaceutical production thus far has been on generator produced ^{225}Ac. This method results in the chemical separation of ^{225}Ac from ^{225}Ra and ^{229}Th. It is therefore very important before obtaining ^{225}Ac to carefully evaluate the possible impurities which may affect the production of the radiopharmaceutical, release criteria and waste handling. This is discussed,

but it is also envisioned that more data will become available in the future once other methods of ^{225}Ac from ^{225}Ra and ^{229}Th. It is therefore very important before obtaining ^{225}Ac to careful production becomes more widely adopted.

Actinium-225 can also be used to manufacture a generator that provides ^{213}Bi as α emitting daughter radionuclide. The short half-life (46 min) of ^{213}Bi further enhances its safety profile, as it minimizes the duration of radiation exposure. These attributes make ^{213}Bi a promising and useful tool in the realm of α therapy, offering a targeted and efficient approach to treating certain types of cancers with reduced collateral damage. High activity ^{225}Ac/^{213}Bi generators are required for the clinical production of ^{213}Bi radiopharmaceuticals. Since the demand for ^{225}Ac is high, very little ^{225}Ac can be spared to produce ^{213}Bi producing generators. At least, this was the case thus far with the major source of ^{225}Ac being from generator produced sources. It is important to note, should ^{225}Ac sources be contaminated with ^{227}Ac, these could be used to produce generators since the ^{227}Ac/^{225}Ac isotopes will be retained on the generator and not be eluted into the ^{213}Bi containing eluate. However, it is important to note that the exact characteristics and breakthrough of such a generator is unknown and should be established. However, the delivery of ^{213}Bi to the target is somewhat complicated by the short half-life thereof, hence clinical adoption is very slow, and research is still ongoing [7]. Hence, for the purpose of this publication, the production of ^{213}Bi radiopharmaceuticals was determined to be out of scope.

The targeted audience of this publication are radiopharmacists, radiochemists and all members of the multidisciplinary team that are involved in making decisions during the implementation of ^{225}Ac into the daily routine practice.

1.4 STRUCTURE

This publication aims to provide the hospital radiopharmacy and other radiopharmaceutical production centres with the latest knowledge to understand the standard operating procedure for the production, QC of ^{225}Ac radiopharmaceuticals. This publication contains 8 sections covering the current state of the art of the production of ^{225}Ac radiopharmaceuticals. To make the outline of themes of the document easier, Fig. 2 provides an overview of the topics covered in this publication with numbers referring to the corresponding sections in the manuscript.

The publication includes sections that will provide information to first time implementors of ^{225}Ac radiopharmaceutical production. This includes some suggestions with regards to infrastructure and staff requirements. The necessary considerations with regards to procurement of raw material are also provided and then a practical guide with regards to the radiolabelling and QC is included.

A small section on future trends is included. A bibliography of resources is provided to the reader for further reading.

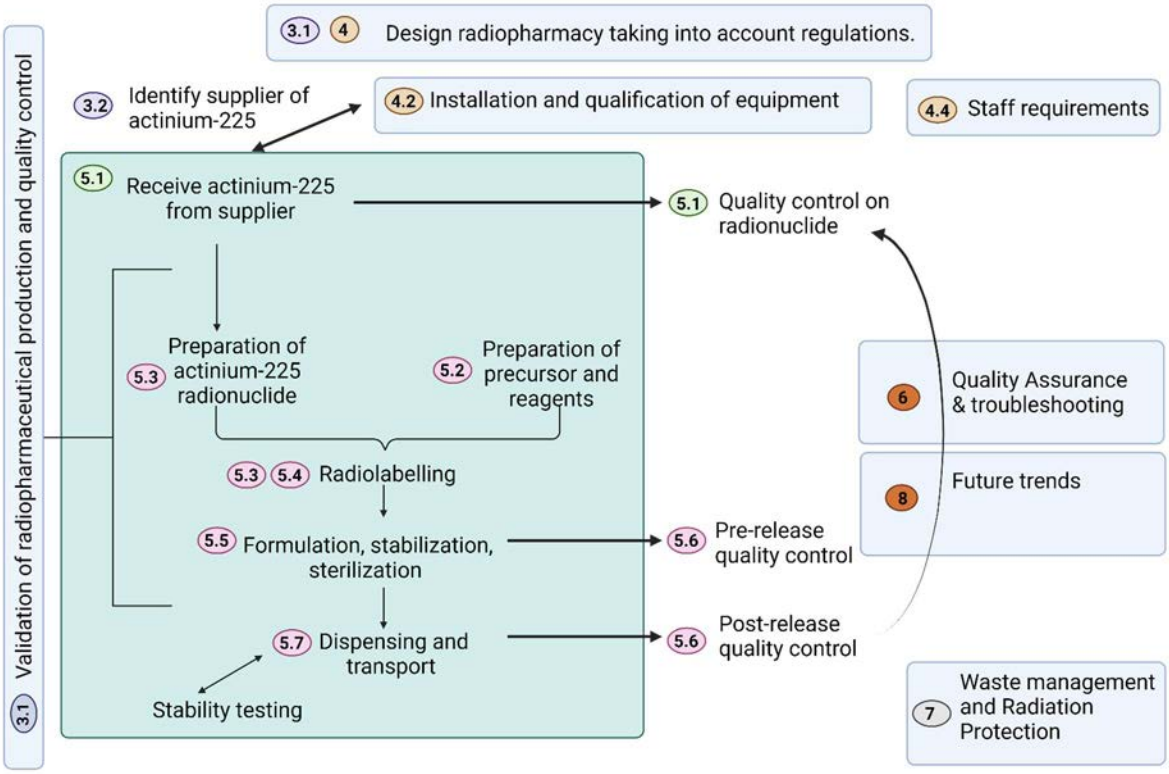

FIG. 2. An overview of the considerations that govern the radiopharmaceutical production of ^{225}Ac (courtesy of J. Kleynhans, KU Leuven).

2. IAEA ACTIVITIES

The IAEA continues to support at least half of its Member States (178 as of December 2023) on the production and application of radiopharmaceuticals through national projects. This contributes the ongoing mission of the IAEA to support peaceful applications of nuclear science and technology, in the sectors of human welfare and health.

2.1 COORDINATED RESEARCH PROJECTS

In October 2018 the IAEA held a two day workshop on the demand and supply of ^{225}Ac. The worldwide need for ^{225}Ac community was estimated. To meet this demand, 3 main production routes were discussed in detail. More than 70 participants from 17 different Member States were present at this meeting, which provided them with a unique opportunity to discuss their work face to face, build and strengthen the existing collaborations. The workshop proved to be extremely useful in addressing the problem of establishing a reliable supply of the promising ^{225}Ac. In September 2019, an IAEA Member States resolution was published during the General Conference, clearly stating Member States intense interest to obtain TAT technology for cancer patients' treatment with a focus on radiopharmaceutical technology.

In a follow up meeting during 9 to 13 December 2019, with the title of 'Technical Meeting on: Production of Alpha Emitters and Radiopharmaceuticals (Ac-225, Bi-213)' in Vienna, the possibility of the production and QC of α emitters using various routes was further discussed by 22 participants from 10 Member States, and it was suggested that an IAEA publication and an IAEA Coordinated Research Project be formulated.

As a follow up, a Consultants' Meeting in June 2021, with a team of experts was held for formulation of a new IAEA CRP within the timeframe 2022–2026, with detailed decisions on the TAT radionuclide as well as CRP participants criteria and aims and scope. It was decided that the CRP should focus on production and QC of ^{225}Ac radiopharmaceuticals, addressing QC, pre-clinical studies, and health regulatory issues, all aspects prior to clinical applications. Also, two IAEA side events during GC in 2021 and 2022 took place with the support of the government of Japan in the field of TAT with a focus on ^{225}Ac and ^{211}At, respectively. The 1st Research Coordination Meeting on ^{225}Ac CRP was held in November 2022 in Vienna with the participation of 24 Member States from 4 continents, the map of participant institutions is shown in Fig. 3.

FIG. 3. Geographical distribution of participating institutes and countries in the IAEA CRP on the Production and QC of ^{225}Ac Radiopharmaceuticals (courtesy of A. Jalilian, IAEA).

2.2. OUTCOMES

The outcomes of the project were:

- Introduction and knowledge transfer for radiochemists and radiopharmacists on the production and QC of α emitting radiopharmaceuticals with a focus on ^{225}Ac;
- Introduction and knowledge transfer for Health Regulators on the production and QC of α emitting radiopharmaceuticals with a focus on ^{225}Ac;
- Introduction and knowledge transfer for radiation safety/waste management authorities' staff at radiopharmacies and application centres on the production and QC of α radiopharmaceuticals with a focus on ^{225}Ac;
- Introduction and awareness for clinicians (oncologists/nuclear medicine physicians) on the availability and possible applications of TAT with a focus on ^{225}Ac.

2.3 OUTPUTS

The major project output was preparation and formulation of this IAEA publication titled 'Production and Quality Control of ^{225}Ac Radiopharmaceuticals' that covers procedures on ^{225}Ac radiopharmaceutical production, QC and the need to develop procedures and protocols for safely working with ^{225}Ac. A baseline is provided for developing facilities to start working with actinium isotopes. A consensus on current practices for QC of ^{225}Ac radiopharmaceuticals is also provided.

Further, the publication includes specifications on ^{225}Ac samples and QC methods needed to be developed for each application and standardised with clearly defined acceptance criteria for the labelled product towards which the participants need to work to ensure the product meets those criteria. The regulatory compliance requirements from different Member States and regional professional societies on utilisation of ^{225}Ac should also be covered and stated as at the time of the release of this publication. It goes without saying that with respect to rapid evolvement of the field, an updated version of this publication will be needed in coming years.

2.4 WORLDWIDE STATUS OF CLINICAL USE OF ^{225}Ac

Research on ^{225}Ac based radiopharmaceuticals has been growing in the last 2–3 decades. This is demonstrated by the increasing number of research papers as can be seen by the keyword search '^{225}Ac' on the PubMed search engine (Fig. 4). It is logical that an increase in research and development will naturally create an increase in clinical trials and finally clinical application. The assumption is of course that the production of ^{225}Ac will be on a scale that the availability is not a limiting factor.

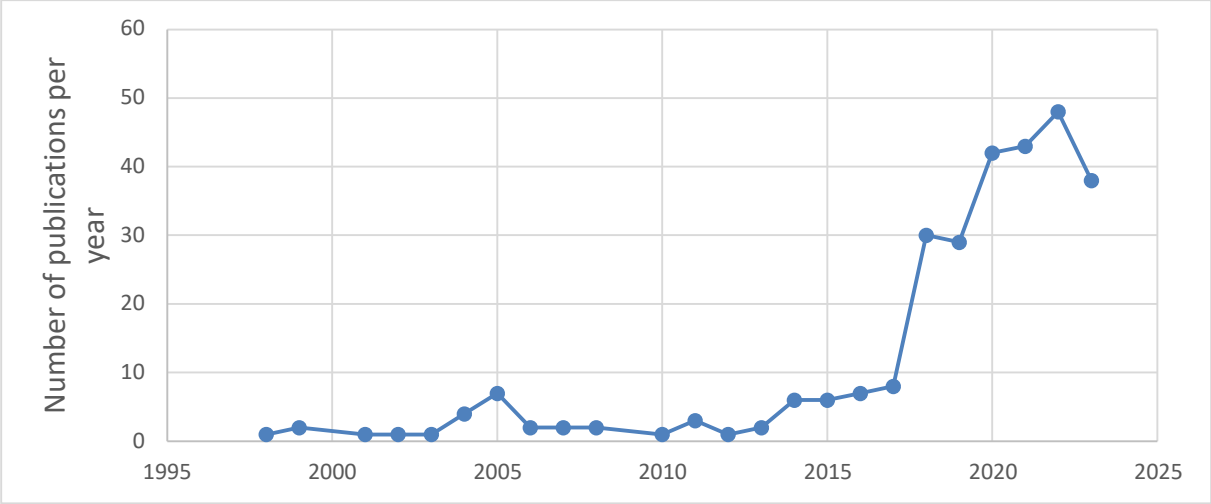

FIG. 4. Increasing number of research papers in PubMed using ^{225}Ac as keyword. The data was obtained for between December 1998 till December 2023 (courtesy of A. Jalilian, IAEA).

The number of registered clinical trials on ^{225}Ac based radiopharmaceuticals is increasing (Table 1). Note that this list is not exhaustive, and that it is out of scope of this document to cover all the applications and uses of ^{225}Ac in clinical and preclinical studies. However, it is interesting to observe the trends in the application of ^{225}Ac and for that purpose a list of current trials registered on clinicaltrials.gov is provided (as of December 2023).

TABLE 1. CLINICAL TRIALS INVOLVING APPLICATION OF ^{225}AC REGISTERED ON CLINICALTRIALS.GOV ON DECEMBER 2023 (Courtesy of E. Cazzola, Irccs)

TRIAL NUMBER	NAME	DRUG	CLINICAL TRIAL PHASE
NCT05496686	Targeted Alpha Particle Radiotherapy for Metastatic Uveal Melanoma	[Ac-225]Ac-MTI-201	Phase I –recruiting [16 participants]
NCT05363111	Phase 1 Trial of I-111/ Ac-225-DOTA-Daratumumab in Patients with Relapsed/Refractory Multiple Myeloma	[Ac-225]Ac-DOTA-Daratumumab	Phase I – Not yet recruiting [15 participants]
NCT05204147	A Phase I Study of Ac-225 Labelled Humanized Anti-CEA M5A Antibody in Patients with CEA Producing Advanced Colorectal Cancer	[Ac-225]Ac-DOTA-anti-CEA monoclonal Antibody M5A	Early Phase I [18 participants]
NCT04576871	Re-treatment Ac-225-J591 for mCRPC	[Ac-225]Ac-J591	Phase I recruiting [33 participants]
NCT04886986	Ac-225-J591 Plus Lu-177-PSMA-I&T for mCRPC	[Ac-225]Ac-J591	Phase II recruiting
NCT03276572	Phase I Trial of Ac-225-J591 in Patients with mCRPC	[Ac-225]Ac-J591	Phase I recruiting [31 participants]
NCT04506567	Fractionated and Multiple Dose Ac-225-J591 for Progressive mCRPC	[Ac-225]Ac-J591	Phase I and II [105 participants]
NCT02998047	A Phase I Study of Lintuzumab-Ac-225 in Patients with Refractory Multiple Myeloma	[Ac-225]Ac-Lintuzumab AC 225	Phase I active, not recruiting [12 patients]
NCT02575963	Lintuzumab-Ac-225 in Older Acute Myeloid Leukaemia (AML) Patients	[Ac-225]Ac-Lintuzumab AC 225	Phase I active, not recruiting [72 patients]
NCT03441048	Lintuzumab-Ac225 in Combination with Cladribine + Cytarabine + Filgrastim + Mitoxantrone (CLAG-M) for Relapsed/Refractory Acute Myeloid Leukaemia	[Ac-225]Ac-Lintuzumab AC 225	Phase I Recruiting [33 participants]
NCT04833517	Prospective REgistry of Targeted RadionucLide TherapY in Patients with mCRPC (REALITY Study)	[Ac-225]Ac-PSMA RLT	Prospective observational [Patient registry]
NCT03746431	A Phase 1/2 Study of [225Ac]-FPI-1434 Injection	[Ac-225]Ac-FPI-1434	Phase I Recruiting [38 participants]
NCT00672165	Targeted Atomic Nano-Generators (Ac-225-Labeled Humanized Anti-CD33 Monoclonal Antibody HuM195) in Patients with Advanced Myeloid Malignancies	[^{225}Ac]Ac-labelled humanized anti-CD33 mAB HuM195	Phase I Completed [23 participants]
NCT04946370	Maximizing Responses to Anti-PD1 Immunotherapy with PSMA-targeted Alpha Therapy in mCRPC	[Ac-225]Ac-J591	Phase I/Phase II [76 participants]
NCT04225910	Clinical Trial of Ac-225-PSMA Radioligand Therapy of Metastatic Castration-resistant Prostate Cancer	An Ac-225containing PSMA targeting radiopharmaceutical	Early Phase I [20 participants]
NCT04644770	A Study of JNJ-69086420, an Ac-225-Labeled Antibody Targeting Human Kallikrein-2 (hK2) for Advanced Prostate Cancer	[Ac-225]Ac-JNJ-69086420	Phase I recruiting [50 participants]
NCT04597411	Study of Ac-225-PSMA-617 in Men with PSMA-positive Prostate Cancer	[Ac-225]Ac-PSMA-617	Phase I recruiting [30 participants]
NCT05219500	Targeted Alpha Therapy with Ac-225-	[Ac-225]Ac-PSMA I&T	Phase II recruiting

TABLE 1. CLINICAL TRIALS INVOLVING APPLICATION OF ^{225}AC REGISTERED ON CLINICALTRIALS.GOV ON DECEMBER 2023 (Courtesy of E. Cazzola, Irccs)

TRIAL NUMBER	NAME	DRUG	CLINICAL TRIAL PHASE
	PSMA-I&T of Castration-resISTant Prostate Cancer		[100 participants]
NCT05605522	A Study of [Ac-225]-FPI-2059 in Adult Participants with Solid Tumours	[Ac-225]Ac-FPI-2059	Phase I recruiting [42 participants]
NCT05363605	A Study of [Ac-225]-FPI-1966 in Participants with Advanced Solid Tumours	[Ac-225]Ac-FPI-1966	Phase I and Phase II Completed [6 participants]
NCT05595460	Study of RYZ101 in Combination with SoC in Subjects With SSTR+ ES-SCLC	[Ac-225]Ac-DOTA-Tyr3-Octreotate	Phase I recruiting [31 participants]
NCT05477576	Study of RYZ101 Compared with SOC in Pts w Inoperable SSTR+ Well-differentiated GEP-NET that has Progressed following Lu-177-SSA Therapy (ACTION-1)	[Ac-225]Ac- DOTA-Tyr3-Octreotate	Phase III recruiting [288 participants]
NCT06052306	A Study to Learn How Safe the Study Treatment Ac-225-macropa-pelgifatamab (BAY3546828) is, How it Affects the Body, How it Moves Into, Through and Out of the Body, and About Its Anticancer Activity in Men With Advanced Metastatic Castration-resistant Prostate Cancer (mCRPC)	[Ac-225]Ac-Macropa-pelgifatamab	Phase I recruiting [140 participants]
NCT05496686	Targeted Alpha Particle Radiotherapy for Metastatic Uveal Melanoma	[Ac-225]Ac-MTI-201	Phase I -recruiting [16 participants]

3. ACTINIUM-225 SOURCE CONSIDERATIONS AND PRODUCTION

At the time of writing this the main source of ^{225}Ac that has been used clinically is derived from the stock of ^{229}Th. However, we aim to provide some considerations on the source of ^{225}Ac from a regulatory framework, as well as a radiochemistry perspective and influences on radiolabelling yields across all possible sources envisioned to become available in the future.

3.1 REGULATORY FRAMEWORK PERTAINING TO ^{225}Ac RADIOPHARMACEUTICALS

Regulatory aspects play a crucial role in ensuring the quality and safety of the preparation of radiopharmaceuticals, particularly in the context of patient care. Especially during the preparation of therapeutic radiopharmaceuticals this is even more important due to the fundamental need to guarantee the effectiveness of treatment and to minimize side effects.

Different regulatory frameworks exist worldwide. While current Good Manufacturing Practice (cGMP) is required for therapeutics on the market, various countries may have different quality production standards for Investigational Medicinal Product (IMP) radiopharmaceutical preparations. Currently, ^{225}Ac based radiopharmaceuticals still largely fall under the umbrella of IMP preparations.

Recently, Europe has implemented the EU Clinical Trial Regulation EU No. 536/2014 [8]. This regulation is mandatorily applied without any modification across all EU member states. It makes a distinction between diagnostic and therapeutic radiopharmaceuticals. Diagnostic radiopharmaceuticals are given certain concessions in productions, as they can be produced by following the regulations present in the respective countries, and in some cases, there may be a downgrade in regulatory requirements. However, for therapeutics, no deviation from cGMP production is allowed [9,10,11].

The Regulation 536/2014 standardizes the European Investigational Medicinal Product (IMP) and clinical trial submission by uploading it to a centralized database. This simplifies the procedure and enables the possibility to expedite the evaluation process. Requests for clinical trial applications are regularly submitted, a list is provided of current registered trials in Table 1.

Implementation of Current Good Manufacturing Practice (GMP) in therapeutic production takes important challenges in the environment of a hospital based radiopharmacy [12-15]. Challenges include dedicated productions laboratories, strong validation procedure for manual production (common with therapeutics IMP applications), radioprotection implementations and supplier validation, all of them, in addition with others, need to be addressed to obtain the regulatory approval. The set-up of laboratories, preparation of procedures, equipment validation, and qualifications are common practices in the application of Current Good Manufacturing Practice (cGMP). However, in the case of ^{225}Ac, some critical points arise for supplier validation, especially for radionuclide producers.

Some points that need additional consideration during therapeutic production that could have implications from a regulatory perspective are listed below:

- Knowledge: There might not be a good set of examples of inhouse health physics guidelines to follow and there may be a need to transfer knowledge to local authorities so that they are informed to be able to provide good guidance. For therapeutic radionuclides like ^{225}Ac, this becomes more challenging;
- Infrastructure: ^{225}Ac has unique requirements due to its decay by α emission. This might require the need for dedicated areas for production;
- Operational: Currently most facilities use manual labelling to produce ^{225}Ac based radiopharmaceuticals. This production method is always more challenging from a cGMP perspective compared to automated methods;
- Radionuclide: Not all the current production sources provide a GMP form of ^{225}Ac. This requires stricter acceptance criteria for the radionuclide;
- QC: There is no stable actinium isotope available, and this makes the validation of QC methods for radiochemical purity complicated;
- Validation: There are unique requirements for the validation of equipment towards detection of ^{225}Ac due to the decay chain and inability to measure α emission directly with current detectors.

Most of the points listed are addressed by this publication, presenting the state of the art in the production of ^{225}Ac radiopharmaceuticals. However, certain peculiarities are dependent on country regulations and availability. This is especially impertinent now until the registration of radionuclide precursors or publication of monographs becomes a reality. One of the most variable aspects of radiopharmaceuticals based on ^{225}Ac is the availability of a reliable source to provide sufficient quantities to meet demand. There is a limited amount of produced ^{225}Ac worldwide, and it is obtained through different pathways with varying quality profiles. These differences can impact the final radiopharmaceutical quality. Therefore, having marketing registered suppliers or a monograph to use as a reference for the quality of ^{225}Ac produced would undoubtedly support and facilitate the IMP development.

In Europe, a request for a monograph for the ^{225}Ac precursor for radiolabelling has been submitted and is currently under revision by the European Directorate for the Quality of Medicines & HealthCare. If the preparation of the monograph begins and is completed, it will simplify the IMP preparation. Additionally, it will provide the ^{225}Ac supplier the opportunity to align with specified quality standards.

In the United States of America, therapeutic radiopharmaceuticals are held to the same stringent cGMP standards as traditional therapeutic drug manufacturers, as described in 21 CFR Parts §210 and §211. These require a more disciplined approach to facility design controls, such as HVAC, utilities, and dedicated aseptic processing considerations with dedicated buffer zones for implementation of sophisticated contamination control strategies, while also requiring higher levels of material/component controls, sterility, and bio burden testing, as well as two operator verification for the manufacture and distribution of late stage clinical drug products and supplier validation. There are United States Pharmacopoeia monographs that could be followed are such as 821 or 825, but nothing that is specific to ^{225}Ac radiopharmaceuticals.

In Europe, there are currently multiple suppliers for ^{225}Ac. One of the most active suppliers of ^{225}Ac is the European Commission's Joint Research Centre, Institute for Transuranium Elements in Karlsruhe. This institution produces ^{225}Ac using an internal produced ^{229}Th generator and supplies, the isotope, as active pharmaceutical ingredient materials with certificate of analysis specifications provided. Other options available for the European market

include Rosatom and the U.S. Department of Energy (DOE). Both entities produce ^{225}Ac through beam irradiation of ^{232}Th, each with a different impurity profile. They supply the product without marketing registration, supplying it as an active pharmaceutical ingredient with an included certificate of analysis. The DOE produces the material under cGMP and files a drug master file with the U.S. Food and Drug Administration for both types of ^{225}Ac that it supplies, and supplies letters of authorization for users wishing to use the material in clinical trials that allow the U.S. Food and Drug Administration to review the DMF with the new drug application.

3.2. ACTINUM-225 PRODUCTION

Currently, the main source of ^{225}Ac that is applied clinically is derived from the stock of ^{232}Th. The ^{225}Ac is isolated from a generator system and provided in high specific activity. Recently, ^{225}Ac produced through the spallation of ^{232}Th has also become available and is supplied monthly through the DOE. Several other production routes are currently under active investigation and in development. In this publication, a brief description of production methods is provided. The main considerations of the source of ^{225}Ac that could influence the radiolabelling procedure is summarized in Table 2 and illustrated in Fig. 5. An in-depth discussion on production methods is not provided in this publication due to the focus being on the production methods of the radiopharmaceuticals themselves.

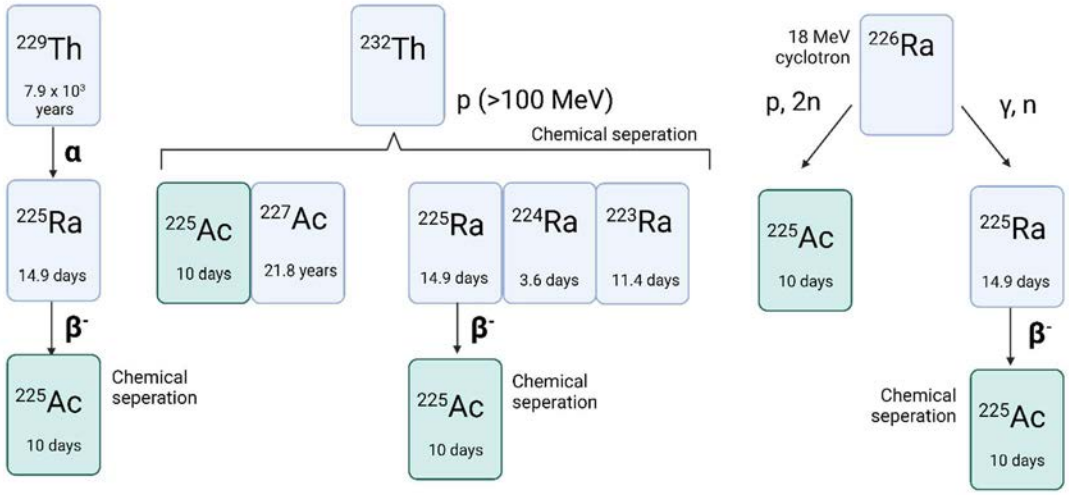

FIG. 5. Schematic overview on the different production methods of ^{225}Ac (courtesy of V. Radchenko, TRIUMF, and of J. Kleynhans, KU Leuven).

3.2.1. Radiochemical separation of ^{225}Ac from ^{229}Th sources

Generator based production is based on 3 main sources available in the United States of America, Russian Federation, and Germany. This is currently the most well known source of ^{225}Ac in terms of performance and application. Many of the methods and considerations provided in this publication are based on ^{225}Ac obtained from this production method. Additional smaller sources of ^{229}Th are available in Canadian Nuclear Laboratories and Belgian Nuclear Research Centre. A total quantity of 1.7 Ci/year of ^{225}Ac is available from this production method from all sources combined [16]. This is a limited amount and not enough to provide for the current demand of ^{225}Ac. Recently, additional sources of ^{229}Th have become available through the commercial company Terrapower from DOE stock extracted from ^{233}U. This has the potential to significantly increase the supply of ^{225}Ac [17].

TABLE 2. DIFFERENT ROUTES FOR PRODUCING ^{225}Ac AND RESULTANT SPECIFICATIONS

	Radiochemical separation of Ac-225 from Th-229 sources	**Irradiation of Th-232 with high energy photons**		**Irradiation of Ra-226 with medium energy protons**	**Irradiation of Ra-226 with photons**
*Current availability	Available	Available	Test quantities available	Not readily available – under development	
Source	ORNL USA IPPE, Russian Federation ITU, Germany CNL, Canada	DOE (BNL, ORNL, LANL), USA TRIUMF, Canada INR, Russia	TRIUMF, Canada		
Radioisotopic impurities to consider	None	Ac-227	None	Ac-226 and daughters, possible trace amounts of Ac-227	Ac-227**
Radionuclidic impurities to consider	Th-229, Ra-225	Spallation products Th-232	Spallation products Th-232 radium isotopes	Ra-226	Ra-226, Ra-225
Main chemical impurities to consider	Iron, zinc, copper decay products (e.g. Bi-209)	Iron, zinc, copper decay products (e.g. Bi-209)	Iron, zinc, copper decay products (e.g. Bi-209)	Iron, zinc, copper decay products (e.g. Bi-209)	Iron, zinc, copper decay products (e.g. Bi-209)

*The green indicates a source that is readily available; orange indicates a product already advanced in development and available in limited quantities or/and from limited suppliers; and red indicates a source not available yet at the time of this publication.
**Actinium-227 can be present in the first Ra-226/Ra-225 elution but is generally removed if the first elution is discarded.

3.2.1. Irradiation of 232Th with high energy protons (100 MeV and above)

Production using the spallation reaction on ^{232}Th with high energy protons (100 MeV and above) has provided an increase in the availability of ^{225}Ac. The irradiation of ^{232}Th can produce significant quantities of ^{225}Ac. However, this method also results in the co-production of many fission products which can be chemically isolated with proper radiochemical process except other isotopes of actinium. The radioisotopic contaminant for the product that remains after purification is ^{227}Ac (physical half-life of 21.7 years) in an amount of less than 1% in terms of activity [4, 18, 19]. However, in terms of radioactive atoms, ^{227}Ac represents almost an equal amount to that of ^{225}Ac and the influence on radiolabelling needs to be considered. Currently, spallation derived ^{225}Ac can be purchased from the US DOE. Spallation reaction can also provide isotopically pure ^{225}Ac by isolation of ^{225}Ra from the spallation mixture. There are multiple radium isotopes produced during this process (including ^{223}Ra, ^{224}Ra and ^{225}Ra). However, only ^{225}Ra decays by β decay to ^{225}Ac and can be separated after equilibrium. While there are a limited number of facilities that have the capacity to accelerate protons above 100 MeV, scaling of production is possible by increasing the mass of the thorium targets, increasing current, and optimizing irradiation time.

3.2.2. Irradiation of ^{226}Ra with medium energy protons (16 MeV): (^{226}Ra (p,2n) ^{225}Ac and with photons (^{226}Ra (γ,n) ^{225}Ra →^{225}Ac)

There is potential to produce clinical quantities of ^{225}Ac by irradiating a ^{226}Ra (physical half-life of 1600 years) with medium energy protons (16 MeV) and photons. The main challenges associated with radium targets are handling and availability. Radium-226 contains several progeny radionuclides in the decay chain with ^{222}Rn (physical half-life of 3.8 days) as radioactive inert gas, which can significantly complicate the target preparation, handling, and further radiochemistry. While there are no available products yet based on ^{226}Ra, several research centres and commercial companies have explored those routes over the past decade.

3.2 THE CHEMISTRY OF ^{225}Ac

The most stable state of actinium in aqueous solution is in the +3-oxidation state and hence it possesses chemical properties that are quite like lanthanide ions. Actinium is the largest +3 ion in the periodic table and has the most basic characteristics. This therefore allows a broader range of labelling pH with hydrolysis not occurring until the pH is greater than 9. This enables the application of more basic buffers with radiolabelling methods reported utilizing Sodium Acetate (pH 5) and Tris(hydroxymethyl)aminomethane buffer (pH 9). Labelling at basic pH can be beneficial to avoid the competition of other cations for chelation [20]. The development of actinium specific chelators has been hampered by the unavailability of a suitable cold isotope and lack of knowledge regarding Ac^{3+} coordination chemistry. However, for clinical application, the DOTA chelator is the state of art and most current radiopharmaceuticals in clinical trials employ this chelator. The application of already developed DOTA based radiopharmaceuticals also allow for easier clinical translation, because of available GMP produced precursors suitable for radiolabelling of metal based radiopharmaceuticals are suitable for patient use. Further, the in vivo behaviour and toxicity of DOTA is well understood.

The use of DOTA as a chelator has some constraints. Firstly, it requires the heating of the labelling mixture, and this might influence the stability of the structure of heat sensitive biological vectors and thus lower its affinity [21]. It is therefore important that during research and development, it is ensured that the vector can withstand heat and is stable. Secondly, the thermodynamic stability of [^{225}Ac]Ac-DOTA constructs are at a disadvantage because of the bigger ionic radius of Ac^{3+}. It is therefore critical that stability studies are performed as part of the inhouse validation process to ensure stability of the manufactured preparation. During the α decay of ^{225}Ac, energy is imparted to the daughter nuclei, and this is theorised to remove daughter decays out of the chelating complex [22]. Additionally, the chemistry of some of the daughters of ^{225}Ac, does not allow stable entrapment into DOTA. The addition of Diethylenetriamine pentaacetate (DTPA) and ethylenediamine tetraacetic acid are critical to ensure that all unlabelled or freed ^{225}Ac and daughter nuclides are captured to ensure the rapid excretion of any free radionuclides.

Currently, new ^{225}Ac specific chelators are under development to provide alternatives that allow for radiolabelling at room temperature. It is important to highlight that the recoil energy is a physical characteristic of the decay behaviour of ^{225}Ac and will most likely not be solved by more advanced chelation. It is envisioned that DOTA will for the time stay the most important clinically applied chelator, and hence, this publication is focused on the techniques in manufacturing radiopharmaceuticals involving this chelator.

4. FACILITY CONSIDERATIONS

Before embarking on the production of ^{225}Ac radiopharmaceuticals, it should be considered that some investment in infrastructure is necessary to allow for the implementation of these methods that is specific for ^{225}Ac.

4.1 DESIGN OR UPGRADE OF RADIOPHARMACY FOR ^{225}Ac PRODUCTION

When the design or reorganization of a radiopharmacy facility is considered in the preparation for starting production of ^{225}Ac radiopharmaceuticals, safety to the operator should be the number one priority. With ^{225}Ac contamination being a main concern – external radiation from the source does not contribute to a high dose rate of the operator in comparison with other radionuclides. Dedicated shielding from sources themselves should be sufficient to shield against radiation emitted from daughter decays. More critically, the contamination risk of ^{225}Ac should be contained and controlled. It is important to perform a radiation risk assessment prior to service commencement.

It is highly desirable to have a dedicated production room and dedicated equipment for ^{225}Ac production, or at least different α emitters pertaining that proper line clearance is performed. This is due to the specialised requirements of the radionuclide for protection as well as the low emissions; even small amounts of other radionuclides (e.g. ^{177}Lu and ^{111}In) will make it difficult to detect the presence of ^{225}Ac for radiation protection monitoring, as well as QC measurements. It is highly recommended that if clinical scale productions are preformed, that this should take place in a glove box (isolator). A hotcell is also a possibility, however the radionuclide does not need the lead shielding provided by the hotcell so this might be an ineffective application of expensive equipment. It is of high importance that all handling, including preparation of QC samples and Instant Thin Layer Chromatography (ITLC) strips, is performed in an enclosure such as a hotcell or glovebox. An example of a facility used to produce ^{225}Ac based radiopharmaceuticals is provided in Fig. 6 and Fig. 7.

FIG. 6. An example of an isolator where radiolabelling of ^{225}Ac based radiopharmaceuticals occur (courtesy of E. de Blois, Erasmus MC).

FIG. 7. An example of a LAF where the heating source (microwave) is housed used during production of ^{225}Ac radiopharmaceuticals, including the dose calibrator for measurement of ^{225}Ac activity (courtesy of E. de Blois, Erasmus MC).

With the isolator providing a grade A environment, the background of the room can be grade C. Pressure gradients as prescribed by GMP guidelines should be followed to provide protection against contamination with ^{225}Ac. While waste management and radiation safety are discussed in Section 7, it is important to highlight that there is some balance to be maintained between radiation safety, and GMP or GRRP considerations. It might be detrimental for radiation protection in the case of ^{225}Ac to split up the QC area and production; all these design factors need to strike a balance between safety and GMP. As an example, for ^{225}Ac higher than typical amounts of activity is needed to obtain a proper TLC, and while the external radiation contamination poses no risk, the spreading of the α emitter and possible risk for inhalation and ingestion should be minimized by putting it in a LAF or fume hood. The facility might not have the capacity to have a dedicated room for ^{225}Ac labelling and a dedicated room with separate LAF for ^{225}Ac QC, and these should be considered. An example of where QC equipment is housed in an LAF is provided in Fig. 8.

FIG. 8. An example of a fumehood where the TLC scanner is housed to perform ITLC scanning with high enough activity to obtain a good chromatogram (courtesy of E. de Blois, Erasmus MC).

It is important to consider the health physics regulations during the design of the process and facility, as depending on the authorities, the amount of activity handled in certain phases of the process could be restricted. Risk assessment on the top of existing infrastructure and day to day workflow should be done. The space within the dedicated workstation for ^{225}Ac production should allow the installation of the automated synthesiser or heating device (heat block or microwave) and additional required accessories (e.g. compressed air).

Waste management is discussed in Section 7, but it also influences the design of the radiopharmacy where the process would influence the design of the waste disposal areas. If the production method introduces long lived radionuclide contamination, it might necessitate additional space for the storage of waste, depending on the local requirements and regulations.

4.2 LIST OF EQUIPMENT AND INFRASTRUCTURE RECOMMENDED

The equipment needed for the radiolabelling of ^{25}Ac based radiopharmaceuticals will be dependent on the planned radiolabelling protocol to follow, local guidelines and regulations pertaining radiation safety, the source of ^{25}Ac, and contaminants involved as well as infrastructure and facility characteristics. However, some suggestions are made in Table 3 that are highly recommended, and Table 4 contains a list of some additional equipment that could be beneficial, which is also recommended in more advanced applications.

TABLE 3. LIST OF REQUIRED EQUIPMENT FOR THE PRODUCTION OF ESTABLISHED ^{225}Ac BASED RADIOPHARMACEUTICALS

Equipment	Minimum Specifications	Comments/Validation to be Performed
Glovebox	For radiation safety two compartments recommended. Grade A with a Grade B hatch to perform safe and according GMP for clinical trials.	All tools and equipment taken out should we tested for contamination first by performing wipe test.
Heating device hotplate	Heating <100°C with temperature monitoring and control.	Validated that accurate and homogenous heating of radiolabelling mixture occur.
Dose calibrator	Allow adjustment with calibration factor to accurately measure Ac-225.	It is recommended to measure a standardised volume in γ counter/ HPGe-detector to perform a cross check against the dose calibrator.
Radio TLC scanner NaI(Tl) detector properly shielded with the possibility of different collimators.	Energy resolution should allow separate measurement of Fr-221 and Bi-213. Detection crystal size and width should allow sufficient count collection.	LOD/LOQ to detected 1% of impurity based on the amount of activity sampled for QC. Linearity in low activity range. Recommended to be placed in a fume hood to be able to increase the activity sampled so that a reasonable quality TLC chromatogram with a relative low amount of activity.
Gamma counter/(i.e. thallium activated, sodium iodide crystal)	Need to separate energy spectra of impurities and decay products.	LOD/LOQ to detect 1% of impurity based on the amount of activity sampled for QC. Linearity across the range of activity used with particular focus on low activity range. Calibrated for Fr-221 and Bi-213.
Endotoxin testing machine	Needs to be easy to use and reduce any risks of contamination. Same specifications as applicable to other radiopharmaceuticals.	Cassette based system recommended, solution for testing should be prepared inside the glovebox.
Filter integrity test	Needs to be easy to use and reduce any risks of contamination. Same specifications as applicable to other radiopharmaceuticals.	Filter test is performed after filtration of the radiopharmaceutical, because of radiation safety should be performed inside the glovebox.
Dedicated micropipette set	Should accurately measure of small amounts below 10 µL. Larger pipettes may also be required during the production process.	Dedicated set which stays inside the glovebox and only taken out for calibration after decontamination.

TABLE 4. LIST OF RECOMMENDED EQUIPMENT FOR THE DEVELOPMENT, CLINICAL TRANSLATION AND PRODUCTION OF NEW ^{225}Ac BASED RADIOPHARMACEUTICALS

Equipment	Minimum Specifications	Comments/Validation to be Performed
Heating device microwave	Allow for the sealed heating of the reaction vial. Cooling function is recommended.	The microwave is recommended from a health physics safety aspect because of the sealed and controlled environment for heating.
High purity germanium Ge detector	Calibrated with a multi-nuclide source covering the energy window of the nuclides to be measured including geometry.	This system is recommended to be used to measure radionuclidic purity. Recommended when radionuclide is obtained from new sources.
Radio HPLC	Including fraction collector to perform indirect measurements for determination of RCP.	When performing radiolabelling of new non established radiopharmaceuticals, it is highly recommended to investigate the RCP and stability by HPLC.
Gas chromatograph	As per normal pharmaceutical specifications.	If the method introduces any chemical impurities that has a prescribed limit (eg DMSO, Acetonitrile).

4.3 VALIDATION OF EQUIPMENT

It is highly recommended to validate the equipment used for the preparation of ^{225}Ac radiopharmaceutical or measurement of ^{225}Ac as a radionuclide according to the European Association of Nuclear Medicine guideline or USP general chapters on the validation of analytical methods for radiopharmaceuticals [23]. Equipment as summarized in Section 2.1 should be validated accordingly.

The amount of radioactivity in comparison with other non-α based therapeutic radionuclides is low. It is therefore important to validate across the ranges of activity, particularly in low ranges of activity, to make sure that it can be accurately quantified. Equipment for activity measurements should only be used at the moment when the ^{225}Ac is in equilibrium with daughters (Section 5.6). Quality measurements, and specifically for QC of ^{225}Ac labelled radiopharmaceuticals are based on gamma detection (^{221}Fr and ^{213}Bi), and therefore used equipment should have the ability to detect specific energy windows separately. For all equipment, the sensitivity of the detectors is critical as the sample volumes are low. QC analysis of ^{225}Ac radiopharmaceuticals is challenging and therefore, the cross-validation of different methods is recommended to ensure quality. As an example, it is recommended that when starting to work with ^{225}Ac, the accuracy of the dose calibrator measurement of ^{225}Ac is cross-validated with a dilution study performed on the γ counter or HP Ge detector, with a source of quantified ^{225}Ac from another facility. An example of a procedure where cross-validation of measuring equipment and a standard ^{225}Ac source is useful, is in the case of measuring a dose of an ^{225}Ac radiopharmaceutical, is provided in Fig. 9.

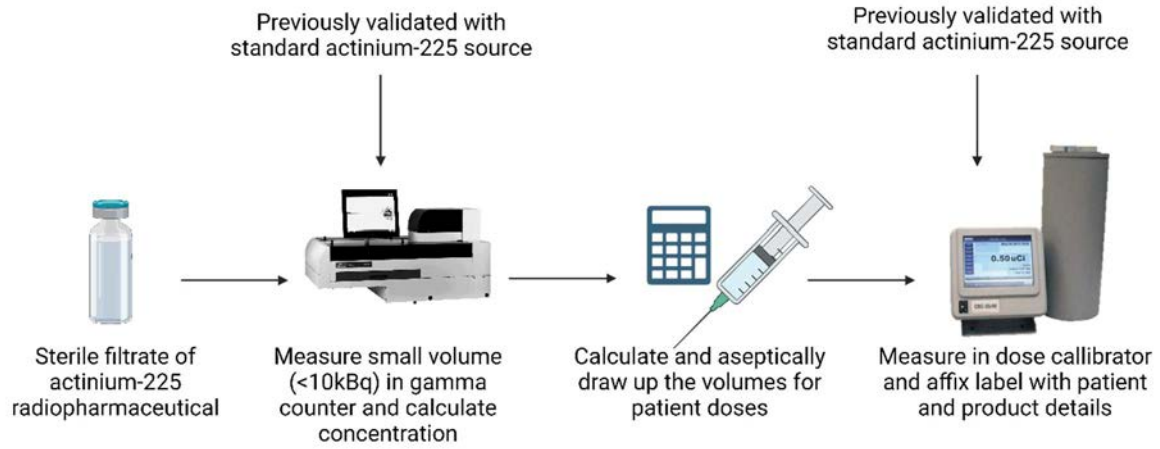

FIG. 9. An example of cross validation of equipment that measures radioactive concentration and is used to dispense the dose of the radiopharmaceutical. Since pharmacopoeia requires a certainty of 5% during dose dispensing, it is critical that the equipment is calibrated correctly. With the low amount of activity measured, validated measuring equipment is important to ensure accuracy (courtesy of E. de Blois, Erasmus MC, and of J. Kleynhans, KU Leuven).

4.4 STAFF REQUIREMENTS

If no member of the staff has prior experience with the production of ^{225}Ac based radiopharmaceutical, it is essential for a senior member of staff to coordinate the introduction and routine management of the new service. It is highly recommended to visit a facility in the region that has already set-up the service. A training programme for staff will be necessary to ensure competency in the new area of work prior to service implementation. Training of personnel should be appropriate to perform the scope of production according to the local regulations of the region. The appropriate training in ^{225}Ac specific radiation protection is also important.

5. RADIOPHARMACEUTICAL PRODUCTION

This section covers the considerations with regards to the radiolabelling ^{225}Ac. The authors attempt to give practical guidance based on personal experience. It is important to note that the source of ^{225}Ac will have an impact on the radiolabelling procedure. Method validation is therefore critical to ensure that reliable radiolabelling of a stable product can be guaranteed, considering the specific infrastructure and raw materials used.

5.1 ACTINIUM-225 AS ACTIVE PHARMACEUTICAL INGREDIENT

When ordering and receiving ^{225}Ac from the selected source, it is important to understand that varying sources can behave differently when used during the production process. This is due to the different combinations of radionuclidic and radiochemical impurities (Refer to table 2).

After the ^{225}Ac source is selected, it is important to carefully plan the production and consider the following:

- The presence of a radioactive licence that allows for the amount of ^{225}Ac to be received, as well as the presence of other radioisotopic or radionuclidic impurities. For this, careful consideration of local regulations and consultation with local authorities is required;
- The consideration of waste management protocols is important and should take into account the radionuclide source;
- The stability of the radionuclide and shelf life thereof is an important consideration. Typically, ^{225}Ac is shipped in the dry nitrate form (preferably in a borosilicate glass vial) to avoid radiolysis and leaching of stable impurities. The amount of time the dry power is stored (from dispensing) is important as to not giving rise to too many impurities. Secondly, the amount of time that the ^{225}Ac can be used after reconstitution in liquid form is also important. The unique constraints offered by the delivery times to the facility should also be considered. Figure 10 provides an example, but note that this is highly dependent on the source of activity and the unique formulation thereof.

A list of possible specifications that the ^{225}Ac active pharmaceutical ingredient should adhere to is provided in Table 5. Note that this could differ depending on the source of ^{225}Ac and the production method thereof. In each case, the source should be evaluated to ensured that it is appropriate to provide a good radiolabelling yield. It should also be established that the source is free from radionuclidic contaminants that can be harmful to the patient. As mentioned in Section 3.1, a request for a monograph for the ^{225}Ac precursor for radiolabelling has been submitted and is currently under revision by the European Directorate for the Quality of Medicines & HealthCare. Once this is approved, clear guidelines with regards to ^{225}Ac as active pharmaceutical ingredient will be established.

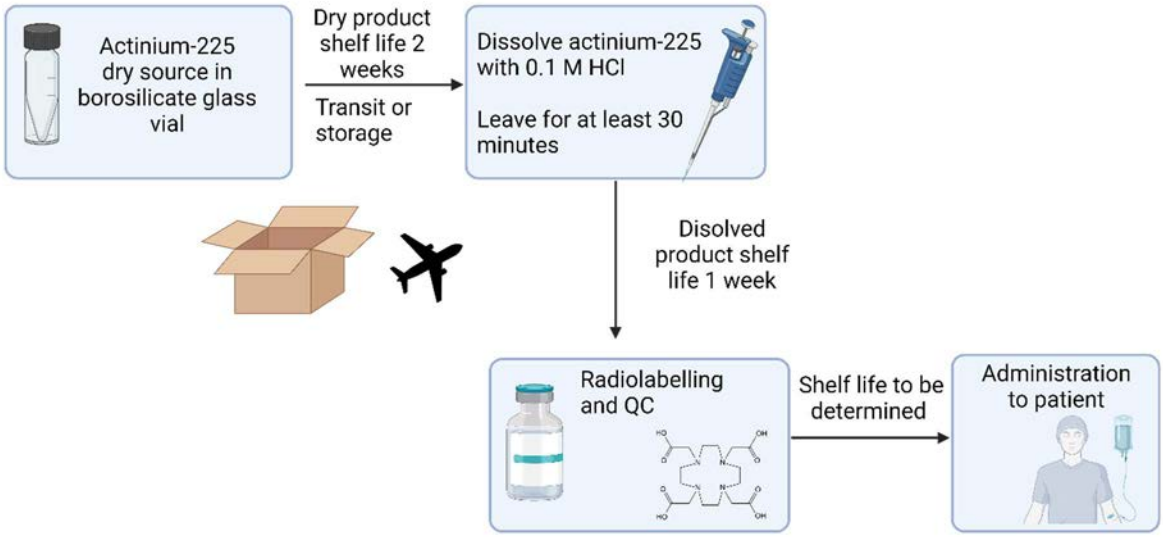

FIG. 10. Schematic overview on the shelf life of ^{225}Ac, based on the ^{229}Th production pathway (according to ITU, Karlsruhe experience & Erasmus MC experience) (courtesy of J. Kleynhans, KU Leuven).

At the writing of this publication, the only GMP quality ^{225}Ac raw material available is supplied from DOE. Therefore, some current applications (preclinical and clinical) rely on the use of non-GMP grade ^{225}Ac. When using a non-GMP compliant radionuclide, it is important that the radiochemical purity thereof is assessed with particular emphasis on the presence of radionuclidic impurities, as well as the presence of metal contamination that can influence radiolabelling efficiency.

TABLE 5. EXAMPLE SPECIFICATIONS OF PRODUCTS THAT IS CURRENTLY AVAILABLE

Example 1: The Institute of Physics and Power Engineering	
Specification	Example product specifications
Form	Actinium Nitrate
Radionuclidic purity	Ac-225 > 99.9% Ra-225 < 0.02%; Radium-224 < 0.002% Other isotopes < 0.0007%
Non-active impurities	< 10 µg/mCi`
Physical form	Dried Solid
Example 2: European Commission Joint Research Centre	
Specification	Example product specifications
Form	Actinium Nitrate
Radionuclidic purity	Ac-225 > 99.98% Th-229/U-233 ≤ 90 ppm Ra-225 ≤ 20 ppm
Non-active impurities	n/a
Physical form	Dried Solid
Specific activity	5.80 x 10^4 Ci/g (theoretical specific activity; carrier free)
Example 3: The Us Department of Energy Isotope Program (Accelerator Material)	
Specification	Example product specifications
Visual inspection	Dry and absent of foreign particles, packed in glass V-vial with solid top screw cap

TABLE 5. EXAMPLE SPECIFICATIONS OF PRODUCTS THAT IS CURRENTLY AVAILABLE

Example 1: The Institute of Physics and Power Engineering	
Specification	Example product specifications
Form	Actinium Nitrate
Radionuclidic purity	Ac-225 > 99% by activity Ac-227 ≤ 2% by activity
Non-active impurities	Available on request
Physical form	Dried Solid
Example 4: The Us Department of Energy Isotope Program (Th-229 Decay Product)	
Specification	Example product specifications
Visual inspection	Dry and absent of foreign particles, packed in glass screw cap bottle in nonreturnable container
Form	Actinium Nitrate
Radionuclidic purity	Ac-225 > 98% by activity Ra-225 ≤ 2% by activity
Radioisotopic purity	100% Ac-225
Physical form	Dried Solid
Specific activity	5.80 x 10^4 Ci/g (theoretical specific activity; carrier free)

5.2 MATERIALS SPECIFICATIONS

Material specifications are influenced by local regulations, as well as the method used to produce ^{225}Ac radiopharmaceuticals. However, some general guidelines are provided here.

5.2.1. Considerations of application for human use

As is the case with manufacturing of radiopharmaceuticals for human use in general, it should be ensured that all materials obtained to produce ^{225}Ac based radiopharmaceuticals are safe for human use. This includes considerations of sterility and toxicity, and all cases should adhere to cGMP requirements as far as possible.

5.2.2. Considerations of metal free production

One of the most important considerations when materials are selected is that the presence of metal impurities deleteriously affect the incorporation of the radiometal (in this case (^{225}Ac) in the chelator system (e.g. DOTA). This is due to the competition of metal ions (eg. iron, copper, zinc) to be incorporated into the chelator. The result of metal contamination can have consequences based on the amount of impurities present, ranging from the need to add more precursor to the mixture to obtain a high radiolabelling yield, up to a total failure of the production of the radiopharmaceutical. Exceptional care should be taken that none of the solutions, raw materials or equipment used before radiolabelling introduce any metals. This is not important for the steps following the radiolabelling (QC, final formulation and dispensing) as the ^{225}Ac should already be incorporated stably in the chelator system.

It is therefore important to eliminate all sources of metals as much as possible and aim for metal free conditions. While it is impossible to reach total metal free conditions, it should be aimed. This starts from ordering all solvents, especially the HCl used for the dissolving of the ^{225}Ac, or other solvents used during the preparation of the radionuclide in super pure form with the

emphasis on metal contaminants. The commercial supplier should provide a CoA stating the amount of metal trace in the composition. Should solutions be prepared inhouse, trace metal ions need to be removed (by for instance using a metal binding resin that binds to polyvalent metal ions and can be filtered out). After solutions are made metal free, care should also be taken that the sterilizing process does not introduce new metals into the system.

Obtaining a completely metal free radiolabelling mixture is not practically attainable and therefore all attempts have to be made to keep the metal contamination as low as possible. As a general guideline, the amount of precursor should be more than twice the amount (nmoles) of the metal impurities. As an example, 60 nmoles of a PSMA compound might demonstrate poorer labelling efficiency if the total of metal impurities in the total formulation exceeds more than 30 nmoles.

All equipment used before and during the radiolabelling should be metal free. Plastic tools instead of metal equipment and needles should be used. Glass vials and labelling vessels can be a big contributor for metal contamination. If metal free sterile glassware cannot be obtained, an inhouse procedure for washing glassware should be established. An example of such a procedure is provided in Fig.11.

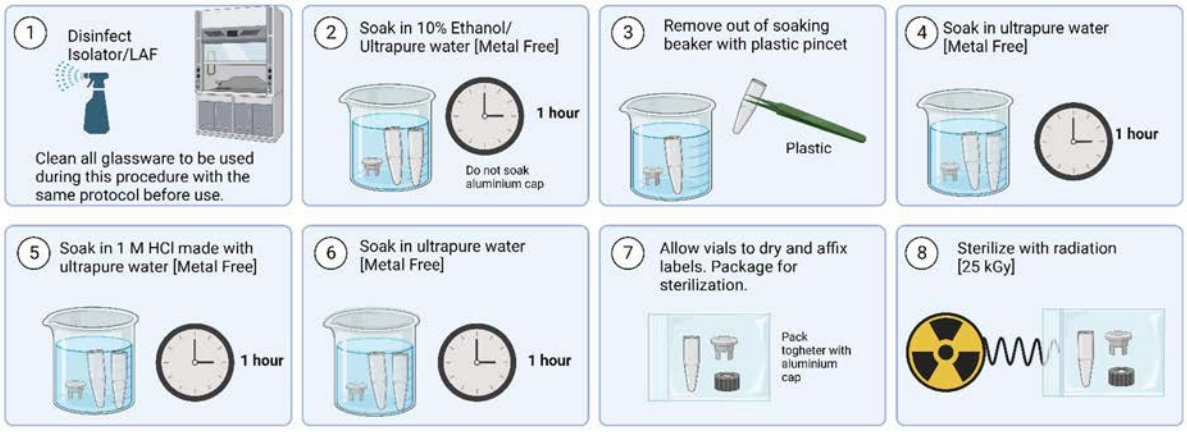

FIG. 11. Example of workflow that is used to prepare glass vials so that they are metal free and sterile (courtesy of E. de Blois, Erasmus MC, and of J. Kleynhans, KU Leuven).

5.2.3. Considerations of sterility

Biological contamination should be restricted by all methods possible. This includes using sterile starting materials and proper aseptic technique. As per cGMP or GRRP principles, aseptic manufacturing should be followed. The presence of endotoxins should also be evaluated, preferably by a cassette based system for the considerations of radiation protection. Other general cGMP or GRRP principles such as bioburden testing and operator qualification with media fills should be performed. Additionally environmental monitoring and qualification of the environment should be performed.

Testing the sterility of the final product could become problematic, as is the case with all longer lived radionuclides. If the facilities to perform sterility testing on α emitter containing radiopharmaceuticals is not available, radiation protection constraints require the decay of the final production vial and for ^{225}Ac this can be up to 200 days of waiting time. With such a long waiting time, the relevance of testing can become controversial as the ability of the formulation to maintain bacterial or fungal growth is questioned. Furthermore, additional contamination is possible during this period. It is suggested that the radiation dose afforded by the α emissions could result in a sterilizing dose, which is contrary to diagnostic radiopharmaceuticals for which

the radiation dose does not equal that of a sterilizing radiation dose [24]. It is however important to consult local regulations as some additional proof might be requested by the local authorities.

Some suggestions of procedures and considerations that are critical are:

— Sterile starting materials;
— Bioburden evaluation of the process;
— Operator qualification via media fills and finger dab tests;
— Environmental monitoring with settle plates.

5.3 RADIOLABELLING OF SMALL MOLECULES

The radiolabelling protocol will differ depending on the radiopharmaceutical being produced, the source of ^{225}Ac and precursors, local radiation protection rules (with regards to the amount of ^{225}Ac that can be handled at one time) and infrastructure available. However, with this section, some general considerations are mentioned. An example of a typical radiolabelling procedure is provided in Fig. 12.

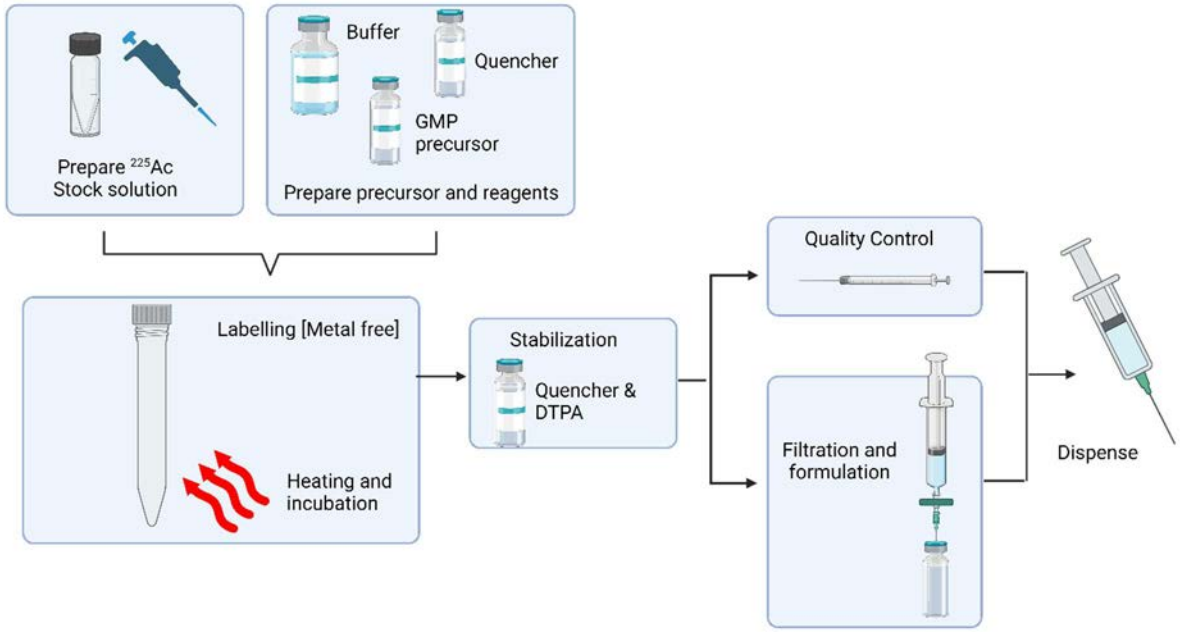

FIG. 12. An example radiolabelling procedure to produce an ^{225}Ac radiopharmaceutical (courtesy of E. de Blois, Erasmus MC, and of J. Kleynhans, KU Leuven).

5.3.1. Preparation of the ^{225}Ac stock

Actinium-225 can be received from the supplier as a dry substance or in liquid form. The form in which it is received will have an influence on how the ^{225}Ac is prepared prior to radiolabelling. Some examples of how to prepare the stock solution is provided in Table 6, however the suppliers instructions should be consulted. Again, it is critical to mention an emphasis is placed on working in 'metal free' conditions during this step. It is also important to ensure that the radionuclide has as little as possible metal–ion contamination. The container in which the ^{225}Ac is shipped could also be a source of metal contamination with increased elution of contaminants due to radiolysis of the vial components, and this should also be considered. The considerations on the stability and the shelf life of the ^{225}Ac, and the reconstituted stock shelf life, should be considered.

If problems are experienced with radiolabelling yield and metal contamination is suspected, the suspect material should be replaced (i.e. consider different shipment or radiolabelling vial). For further instructions refer to troubleshooting section of this publication.

TABLE 6. EXAMPLE OF A METHOD FOLLOWED TO PREPARE THE ^{225}Ac STOCK SOLUTION FOR RADIOLABELLING

Source	Example Method of Preparation
Generator produced Ac-225$(NO_3)_3$. Shipped in dry powder form in a Type I borosilicate glass V Vial.	The activity is dissolved in an acidic solution (i.e., 0.1 M HCl) and incubated at ambient temperature for at least 30 min.

5.3.2. The components of the radiolabelling mixture

The components of the radiolabelling mixture can differ depending on the optimized and validated protocol. It is also perceived to change in the future based on advances in technology in the field or with the development of new radiopharmaceutical vectors and chelators. However, some examples of excipients that can be considered are provided in Table 7.

TABLE 7. POSSIBLE EXCIPIENTS INCLUDED DURING RADIOLABELLING AND THE ROLE THEREOF (courtesy of E. De Blois, ERASMUS MC) [25].

Excipient/Component	Role
Hydrochloric acid	To dissolve dry Ac-225 nitrate. Not included if the Ac-225 is obtained in another form.
Labelling buffer	This is to ensure the correct pH for efficient radiolabelling. Examples are Tris(hydroxymethyl)aminomethane buffer (pH 9) for labelling in basic conditions or Sodium Acetate for labelling in more acidic conditions.
Ascorbate	This is an example radioprotector that can be used as quencher to afford some protection against radiolysis.
DTPA	To ensure that all unbound radionuclides are complexed and excreted by the kidneys in the patient
Saline	To dilute the radiopharmaceutical formulation while it is ensuring osmolality is maintained.

5.3.3. Addition of ^{225}Ac to radiolabelling mixture

The addition of ^{225}Ac is a critical step during production. This should be done last (after all the other components of the radiolabelling mixture has been mixed) just before incubation of the radiolabelling mixture. Incubating the precursor without the presence of quenchers/radioprotectors can cause the formation of unwanted radiolysis products and influence radiolabelling yield substantially.

The addition of the ^{225}Ac should be done accurately and this relies on the accuracy of measuring pipettes, homogeneity of the ^{225}Ac solution (waiting time of at least 30 min post-addition of 0.1 M HCl) and accurate measurements of activity concentration of the source vial. Gentle and carful shaking of the vial could assist with homogeneity.

5.3.4. Stabilization of the ^{225}Ac radiolabelling mixture

The stabilization of the ^{225}Ac radiopharmaceutical already starts during the radiolabelling process by adding the quencher before the addition of ^{225}Ac (Fig. 13).

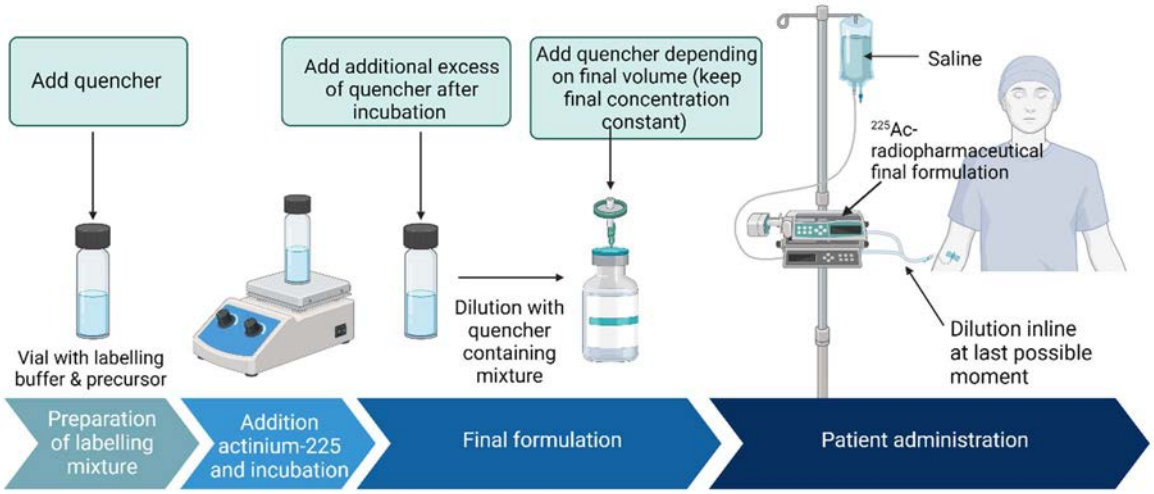

FIG. 13. An example of a workflow that consider the stability of ^{225}Ac radiopharmaceuticals from labelling through to patient administration (courtesy of E. de Blois, Erasmus MC, and of J. Kleynhans, KU Leuven).

It is important to note that the quencher needs to be added in every instance that the radiolabelling mixture is diluted or reformulated as to ensure that a concentration that would provide adequate protection against radiolysis is maintained.

5.4 RADIOLABELLING OF ANTIBODIES

The radiolabelling of antibodies with ^{225}Ac requires a minimum of 2 steps. This is due to the sensitivity of the antibody to the higher temperatures often required to reach high yields of incorporation of ^{225}Ac into the chelator. Both DOTA and DTPA have been evaluated for this application, with DOTA demonstrating the higher stability. The bifunctional chelator can either be radiolabelled in the first step with high temperature, and then in the second step attached to the antibody. However, in some cases the chelator has initially been attached to the antibody and the radiolabelling performed after at lower temperatures and longer reaction times.

In radiolabelling antibodies with ^{225}Ac, it requires the attachment of the bifunctional chelator to the antibody by using a method that does not result in the loss of affinity, which should be validated. A method commonly used, but by no means the only method, is the conjugation of p-SCN-Bn-DOTA to the antibody at random lysine groups by thiourea bond formation. This is done by incubating an excess of the p-SCN-DOTA with the antibody at 37ºC at a pH 9 for a minimum of 1 h. The time should be evaluated to determine what results in the best yield. Addition of DTPA to complex any free metals and then the mixture is purified by size exclusion chromatography. Next, the resultant chelated antibody in buffer and quencher, as recommended above, is radiolabelled with ^{225}Ac at 37ºC for 2–4 h. Again, the incubation time should be optimized dependent on the given antibody and chelator prior to purification by a desalting column. Parameters such as buffer, time and volume should be optimized to give the highest yield that does not diminish the required affinity of the antibody for the target that should be validated.

Important things to consider, as is stated above, is the amount of quencher to ensure stability throughout the process. It might be necessary to add agents such as HSA to minimize absorption of the antibodies to glass or plastic. There are various examples of methods in the literature, but they should be validated for the given targeting antibody under investigation.

5.5 FINAL FORMULATION

For the final formulation of ^{225}Ac radiopharmaceuticals, it is important that a physiological acceptable formulation is reached. The followed procedure will be largely dependent on the method followed during radiolabelling. However, some suggestions are provided based on experience by the authors. It is highly recommended that the dilution of the final formulation is done with the addition of quencher (such as ascorbate) to a concentration in the final formulation that will provide adequate protection against radiolysis. For example, a final concentration of 0.5 M ascorbate and 5% ethanol in the final formulation was found useful for ensuring stability of small molecule based ^{225}Ac radiopharmaceuticals [25].

After, dilution sterile filtration (0.22 μm) is suggested. It is highly recommended that additional safety precautions are taken when the bubble point test for filter integrity is performed as this is a procedure that could result in the contamination and possible ingestion of ^{225}Ac by the operator.

The addition of DTPA is critical to ensure that all unbound radionuclides are complexed and excreted by the kidneys in the patient. It is therefore recommended to always add an excess of DTPA in the formulation of ^{225}Ac radiopharmaceuticals, after radiolabelling is completed.

Dilution of the radiopharmaceutical (considering the concentration of the quencher) is normally done in different phases. An example of such a process is provided in Fig. 13. A possible way is to dilute with saline after radiolabelling followed by a final dilution during administration to the patient.

5.6 EQUILIBRIUM AND APPLICATION IN DETERMINATION OF RADIOCHEMICAL PURITY

At the current time, there are no assay for the direct and accurate measurement of the α decay of ^{225}Ac. HPLC analysis with scintillation counting is complex due to the presence of many α decay daughters (Fig. 14), making the indirect measurement of γ emitting daughters ^{221}Fr and ^{213}Bi the most accurate ones [25].

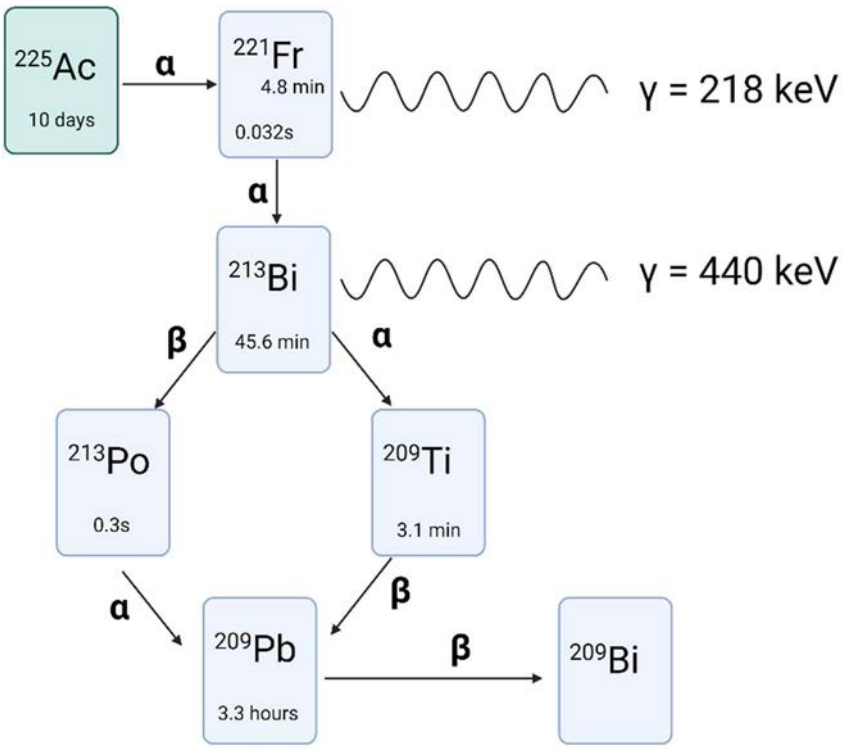

FIG. 14. Decay scheme of ^{225}Ac demonstrating the γ rays of the useful decay daughters (courtesy of J. Kleynhans, KU Leuven).

A secular equilibrium develops after 6 half-lives of the daughter to be measured. This means that an equilibrium is formed between ^{225}Ac and ^{221}Fr/^{213}Bi and that the ratio (98% of ingrowth of ^{221}Fr at 30 min) are at a point where the presence of ^{225}Ac can be accurately determined and quantified (Fig. 15).

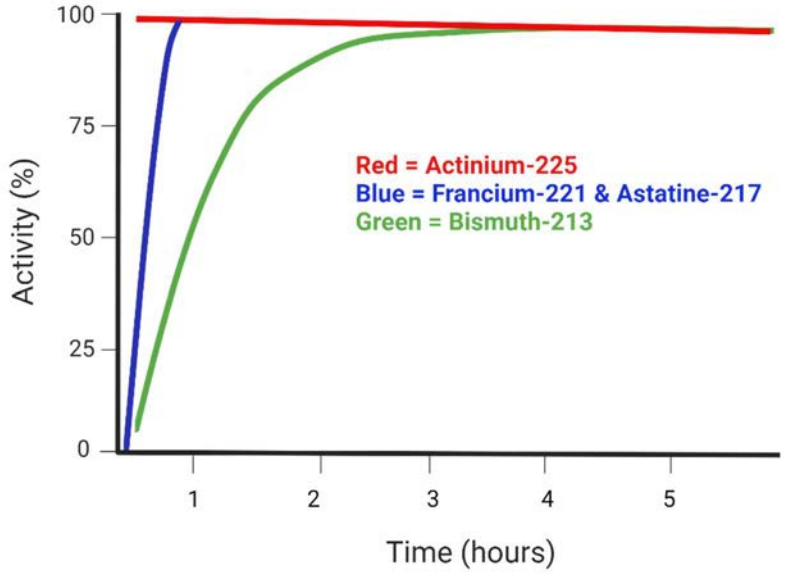

FIG. 15. Activity concentration of daughter radionuclides over time (courtesy of E. du Blois, Erasmus MC).

It is important to note that these methods are highly product (radiopharmaceutical) specific and that every facility should also validate these methods to ensure that all radioactive species can be separated and identified. Again, it is highly recommended to follow the European

Association of Nuclear Medicine guideline or USP General Chapters on the validation of analytical methods for radiopharmaceuticals [23].

For the evaluation of radiolabelling yield for ^{225}Ac based radiopharmaceuticals with ITLC, glass microfiber chromatography paper impregnated with a silica gel is often used as stationary phase. Solutions of sodium citrate as mobile phase (with varying molarities and pH described in literature) is used to distinguish between unlabelled ^{225}Ac and [^{225}Ac]Ac-radiopharmaceutical, while a second mobile phase system consisting of acetonitrile/water could be added to also distinguish [^{225}Ac]Ac-chelate species. An example of a workflow process for the evaluation of radiochemical yield by ITLC that could be followed is provided in Fig. 16.

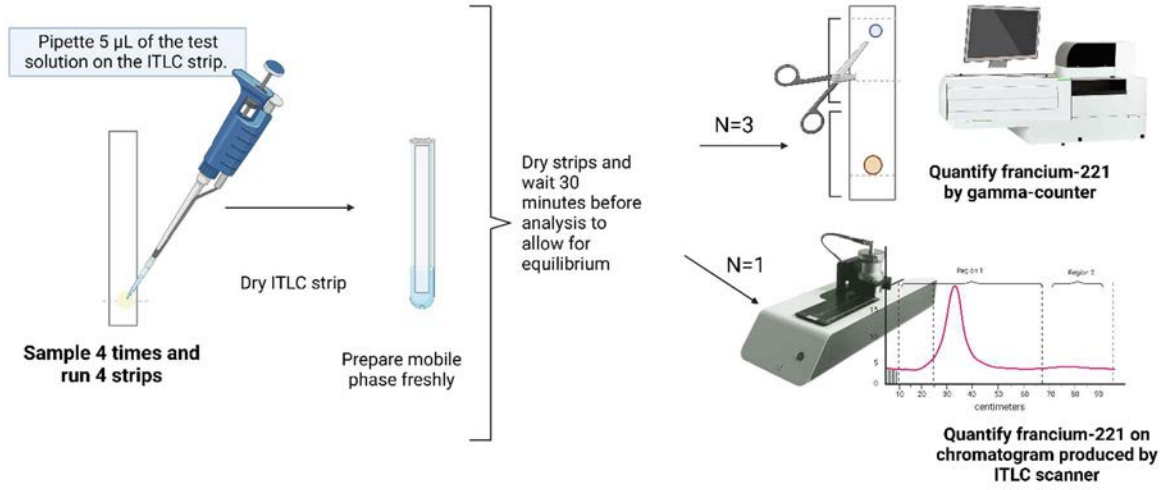

FIG. 16. A possible workflow process for the evaluation of radiochemical yield of ^{225}Ac radiopharmaceuticals with ITLC (courtesy of E. de Blois, Erasmus MC, and of J. Kleynhans, KU Leuven).

It is important that after separation of the radiochemical species on the ITLC strip, that at least a 30 min waiting time passes before analysing the ITLC strip to ensure that the secular equilibrium is reached. The difference in analysis results between immediate measurement and after secular equilibrium is demonstrated in Fig. 17.

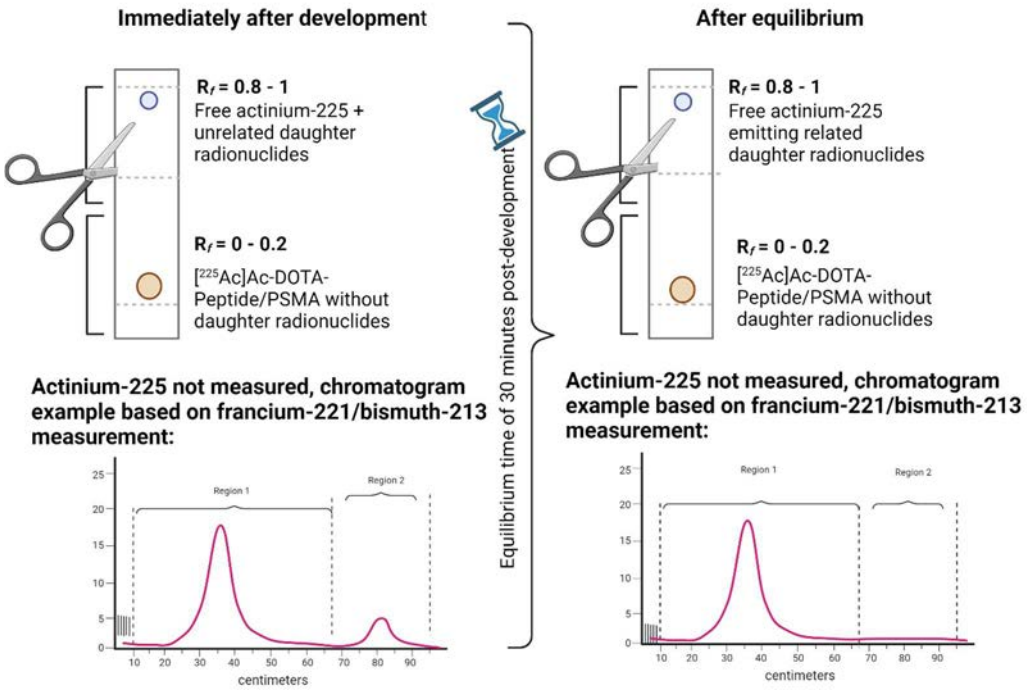

FIG. 17. The differences in measurements after equilibrium time (courtesy of J. Kleynhans, KU Leuven).

Since it is well known that ITLC offers limited sensitivity for the detection of degradation of products, it is highly recommended to implement an appropriate HPLC method during the validation process of the production implementation of a new ^{225}Ac based radiopharmaceutical. Due to the time consumption of this method, it is not recommended for the routine pre-release QC of ^{225}Ac radiopharmaceuticals. However, it is highly recommended to perform this during the validation phase of ^{225}Ac production implementation, as well as post-release of routine productions as part of data collection for quality assurance processes. It is suggested to follow the European Association of Nuclear Medicine guideline or USP general chapters on the validation of analytical methods for radiopharmaceuticals. The system relies on separation by an appropriate HPLC method, fraction collection, waiting at least 30 min for equilibrium to be reached and then measurement in the gamma counter. An example workflow is presented in Fig. 18.

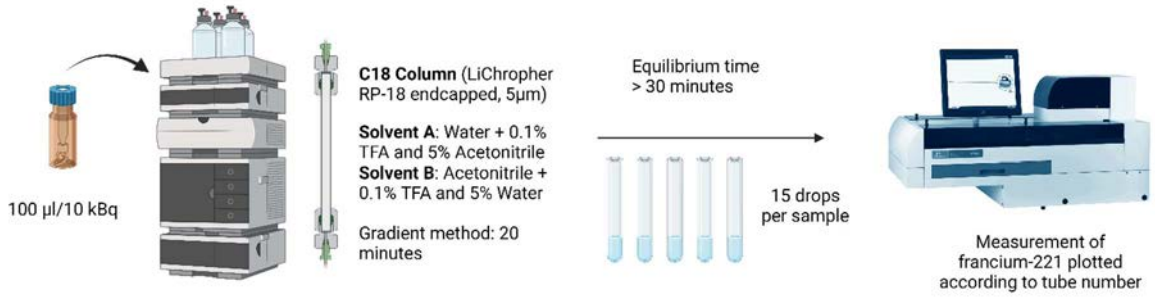

FIG. 18. An example workflow for the analysis of [^{225}Ac]Ac-radiopharmaceutical radiochemical purity by HPLC through indirect measurement of daughter decay (courtesy of E. de Blois, Erasmus MC, and of J. Kleynhans, KU Leuven). [24,25].

The fractions are then counted and plotted to compile a chromatogram, of which an example is provided in Fig. 19.

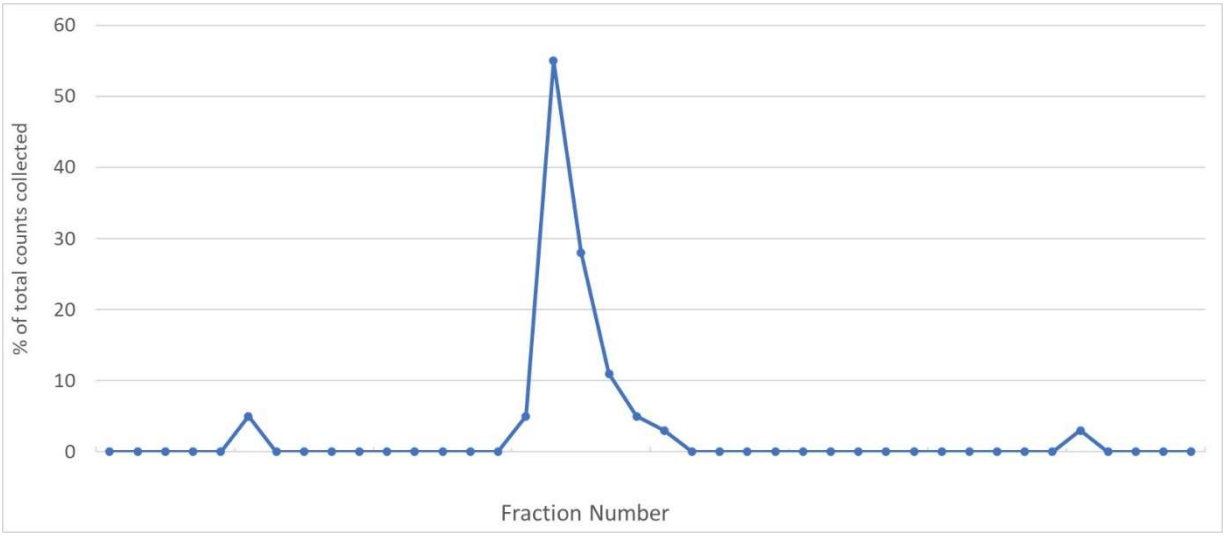

FIG. 19. An example of a chromatogram that is composed from measurements done on fractions collected during radio-HPLC measurement of [^{225}Ac]Ac-I&T (courtesy of E du Blois, Erasmus MC, [24,25]).

5.7 QC OF RADIOPHARMACEUTICALS

In general, a set of predetermined release criteria should be established before validation of radiopharmaceutical production takes place. Some suggested criteria are provided in Table 8 and Table 9.

TABLE 8. LIST OF SUGGESTED PRE-RELEASE SPECIFICATIONS FOR THE QC OF SMALL MOLECULES AND PEPTIDES

Test	Release Criteria	Suggested Method	Notes
Visual inspection	Clear, colourless and free of particulate matter.	According to GMP guidelines.	A yellow solution might indicate a breakdown of ascorbate.
Radiolabelling yield	>98%	ITLC	
pH	5–9	pH strips	Depending on osmolality pH range should be determined.
Pyrogenicity testing	< 5 EU/mL	Cassette based endotoxin test system.	
Filter integrity test	≥3.5 bar	Bubble test	Validation: test on matrix first.
Ethanol concentration (if part of method)	< 10%	Calculation	Calculation is done because of the risk associated with GC contamination.

TABLE 9. SUGGESTED POST-RELEASE SPECIFICATIONS FOR INCLUDING IN QUALITY ASSURANCE PROGRAM

Test	Release Criteria	Suggested Method	Notes
Radiochemical purity	> 95%	Radio-HPLC	It is highly recommended that HPLC is performed for every batch. It is however not feasible to perform HPLC during clinical productions as a pre-release QC due to time constraints.

6. RADIOLABELLING TROUBLESHOOTING

This publication focuses on the safety and implementation of ^{225}Ac. The point by point description will help users to do so but it requires some troubleshooting. In this section, an overview is given of daily practice from the experts with the intention of providing guidance.

6.1 ACTINIUM-225 STOCK CONSIDERATIONS

Depending on the source, variation in outcome of the radiolabelling method can be expected. The ^{225}Ac should be inspected carefully. The vial should be clear and clean without any particles. Darkened glass is a result of high radiation, and this often results in additional impurities that could lead to lower radiolabelling yield. Often, when low labelling yields are found, it is highly likely the result of impurities coming from the ^{225}Ac source. Therefore, the source of ^{225}Ac should often be the first step to revisit during an out of specification investigation. A good supplier would have performed stability studies to demonstrate that no metals are introduced into the ^{225}Ac from the packaging, up to the indicated expiration date.

6.2 STARTING MATERIALS

Low labelling yield can also be the result of impurities coming from any of the raw materials that are used during the production method. The labelling method should be standardized and validated, and the addition of any new chemicals should lead to an additional validation to check the influence of the specific chemical individually. Purity of the chemicals can also be measured by titration as described [25]. Pre-purification of the chemicals might also be an option (i.e. by use of chelex to remove metals or the use of an acidic wash to purify glass containers) but should be well validated.

6.3 LOW YIELD AND PURIFICATION

When low labelling yields are obtained, it is recommended to first optimize the radiolabelling protocol if possible and to avoid reliance on a purification method. Purification has additional constraints in the production of ^{225}Ac radiopharmaceuticals with regards to radiation safety.

Should purification be attempted, this can either be done by SPE purification or by semi-preparative HPLC. It should be noted that when performing purification, the method should be validated to prove efficacy. Lower yield would preferably be purified by SPE purification, while oxidized or radiolysis products should be excluded by performing HPLC purification. It should be noted that after purification, quenchers have to be added again as they will be excluded by purification as well. The correct concentration of quencher, as mentioned before, is extremely important to maintain the integrity and stability of ^{225}Ac containing radiopharmaceuticals.

Again, it should be highlighted that ^{225}Ac has additional requirements with regards to radiation protection. It is recommended when HPLC purification should be performed, this should be done with a dedicated purification system, which is housed inside a fume hood or glovebox.

6.4 STABILITY

The stability of ^{225}Ac radiopharmaceuticals is highly important as it has been proven that minor impurities might have a major impact in vivo. The validation of stability by monitoring of the radiochemical purity over time is critical. This validation of stability should be performed by HPLC because radiolysis products are often not visible on ITLC. Because of radiation safety,

only a low amount of ^{225}Ac can be injected onto the HPLC system. The lower the injected amount, the higher the possibility of retention on the column and higher the impact on the outcomes (false positive/negative). This makes the measurement of recovery very important, and this procedure should not be neglected.

6.5 GMP AND NON-GMP

Since ^{225}Ac is an α emitter, many challenges should be overcome as touched upon in this publication. To be able to work safely, regarding radiation safety measures and excluding issues regarding product quality, it is highly recommended to work via GMP approach even during the development state. The use of GMP complaint raw materials (such as labelling precursor) is also highly recommended as this will standardize the labelling process and negate many possible sources of error.

7. RADIATION PROTECTION CONSIDERATIONS

The main concern while using α emitters is not the external radiation but rather the risk of contamination and more specifically ingestion. Actinium-225 is known for high energy emissions and resulting toxicity. Special handling is required, and additional challenges are present, especially when production of the radiopharmaceutical is upscaled to patient dosing. To minimize possible risks, a radiation risk assessment is required to ensure the safety of the staff who perform the production process. A dedicated laboratory for the radiolabelling of α containing radiopharmaceuticals is highly recommended.

When working with ^{225}Ac, small contamination in analytical systems or at working spaces may have a major impact. Since α radiation can be highly radiotoxic, the health physics regulations should take this into account. This is a limiting factor towards the amount of activity that can be handled. This could for instance, be that only a few kBq (<10 kBq) can be allowed for QC measurements in a regular class laboratory.

7.1 SHIPMENT OF ALPHA EMITTERS

Influence of the source of ^{225}Ac production on the regulations should apply to the shipment procedure. There are expert controls in place that should be referred to for shipping radionuclides and radiopharmaceuticals. The regulations are regions specific, and, in most cases, guidance should be developed to ensure that export control is not violated. Further dependent on how the material is meant to be used, it may be necessary to register with the local regulatory agencies, such as the FDA in the US.

7.2 HAZARD ASSESSMENT OF CONTAMINATION

When the decision is made to start production of ^{225}Ac based radiopharmaceuticals, a risk assessment should be performed. Clear guidance on risk assessments is provided in the IAEA General Safety Requirements (GSR) part 4 [27] and ICPR 1990, ICPR 2007. The risk assessment should focus on the hazard of contamination. It is a critical aspect of radiation protection and nuclear safety, and should include inputs from a multidisciplinary team (e.g., radiation safety experts, health physicists, environmental scientists, and regulatory authorities [28,29].

The source of ^{225}Ac and production route to be followed, will have an impact on the radiation safety and waste management processes. The decay chain of ^{225}Ac as well as the consideration of long lived progeny or impurities should be carefully considered. The risks associated with the use of α emitters should be negated to protect both human health as well as the environment. This should include regular surveying practices with the proper radiation instrumentation and correct methods for decontamination [28,29].

The key steps to assess the hazard of contamination with α emitters are provided:

- Identification of the specific α emitting radionuclides involved and characterization of their properties. This includes half-life, decay chain and energy of emitted α particles;
- Determination of the source of α contamination;
- Conducting radiation measurements to assess the extent and intensity of contamination by using α detectors, liquid scintillation counters or other specialised instruments able to measure α radiation levels;

— To create contamination maps to visualize the distribution and concentration of α emitters in the affected area to identify hotspots and areas of concern;
— Evaluate potential pathways through which individuals may be exposed to α radiation, including inhalation, ingestion, direct skin contact and external radiation;
— Consider the biological effects of α radiation, including the high relative biological effectiveness of α particles, which involves assessing the potential health risks associated with exposure;
— Determine applicable regulatory limits and guidelines for α emitters based on the specific limits and dose criteria indicated by the national or local health physics authorities;
— Apply dose modelling and calculations to estimate the dose received by individuals in the affected area, based on exposure scenarios and the measured levels of contamination;
— Conduct a risk assessment to estimate the likelihood and consequences of exposure to α emitters, considering the dose received, exposure pathways and the presence of sensitive populations;
— Develop and implement strategies for mitigation and remediation of contamination by including for example decontamination procedures, sealing the source, or implementing controls to prevent further spread;
— If the contamination presents an immediate hazard, initiate emergency response measures;
— Communicate information about the contamination and risks effectively to the affected individuals, worker community and relevant stakeholders;
— Implement a long term monitoring program to assess the effectiveness of remediation efforts and track any changes in contamination levels over time.

7.3 WASTE MANAGEMENT

The important activities to manage the waste generated from ^{225}Ac radiopharmaceutical production are the following:

— Minimizing the amount of waste created;
— Proper characterization of the waste and its contents;
— Conditioning and packaging to permit safe handling and protection during transport;
— Interim storage;
— Final disposal.

The management of ^{225}Ac waste should happen promptly and continuously. The first critical step is to receive good documentation from the supplier. This should highlight the presence of long lived radionuclides. It is important to also understand the regional specific requirements and guidelines with regards to handling of radioactive waste. Possible long lived nuclides in ^{225}Ac could include ^{226}Ra, ^{229}Th and ^{225}Ac, but the content and amount will depend on the production method and purifications performed on the radionuclide by the supplier. It is critical that for any source of ^{225}Ac (except for generator produced ^{225}Ac from ^{229}Th), that the content of ^{227}Ac should be clearly indicated. In several countries, the waste limit for ^{227}Ac is particularly low and this can become problematic during waste management [30].

It is important to determine if local regulations allow for the storage of material and components used during ^{225}Ac production for temperature storage, and then later free class and release this material as cold waste. It could be possible that thorium containing material should be shipped

to a depository as radioactive waste. Storage of ^{225}Ac contaminated material for 100 days will reduce the activity by a factor of 1000, while storage for 1 year will reduce the activity by a factor of more than 1 million. If regulations require that all material should be deposited at a depository, the availability of a satisfactory deposit needs to be verified.

For handling of patient excreta, again it is important to consult local health physics authorities on which methods are required. This could be waste dilution or decay methods [31,32]. If the country allows the disposal of liquid waste directly in the sewage system without a holding period, it remains the responsibility of the hospital to minimize the consequences of any release and verify the discharges by regular monitoring [33]. A radiological impact assessment is recommended to assess the pathway of exposure and assess doses to any critical workers (such as sewage plant personnel) as well as the dose to the public from fishing or drinking in rivers. The impact on wildlife should also be considered [33, 34].

7.4 FACILITY REQUIREMENTS FOR HANDLING ^{225}Ac

A dedicated hood (e.g., a glovebox) is highly recommended for the manual handling of ^{225}Ac. This reduces the contamination risk for the operator and the potential cross contamination from other radionuclides used in the facility.

If a microwave or larger heating equipment is used during the production of ^{225}Ac radiopharmaceuticals, this should preferably be installed in a separate cabinet. The presence of large equipment in the hood where ^{225}Ac labelling takes place, will disrupt the airflow and might reduce the aseptic conditions.

7.5 GENERAL RADIATION PROTECTION PRINCIPLES

Alpha emitters are radionuclides that pose a significant health risk when inhaled, swallowed, or absorbed into the blood stream through wounds. Clear contingency plans and procedures should be in place to deal with radioactive spills. Any such events should be controlled promptly and effectively. A radiation spill kit should be present during the manipulation of ^{225}Ac in any capacity.

In some regions, continuous air monitoring is required during the handling of α emitters. This can be accomplished using continuous air monitors in the area where the work is being performed, such as those offered by Mirion that can monitor in real time air borne α emitters or can be accomplished by workers wearing devices that monitor in real time air borne α emitters. Furthermore, hand and foot monitors or whole body counters that can detect α emissions should be considered to ensure workers are not contaminated prior to leaving their workspaces in certain regions this maybe a requirement.

Storage of ^{225}Ac prior to use or prior to treatment, should be done to shield from all the daughter decay to a reasonable extent. When ^{225}Ac is labelled manually, procedural items (e.g., long-handled tools or shielded syringes) and shielding may be used to minimize extremity radiation, but it should be noted that this is often unnecessary for the lower activities being used. The sources of external radiation during production are the daughter isotopes ^{221}Fr and ^{213}Bi, but the yields are lower than traditional diagnostic radionuclides.

The use of disposable tools during production are highly recommended. Note that metal free considerations are still very critical and should be considered when choosing these items. Using replaceable mats on the work surface that can be disposed afterwards is highly recommended. All used surfaces and equipment should be monitored after production by taking wipes tests so

that low counts can be measured effectively. Measurement with an α probe is also recommended as this effectively detects small measurements of α particles.

During radiolabelling of precursors with ^{225}Ac, it is recommended to measure the activity concentration in indoor air at the workplace, in combination with other monitoring methods for regular incorporation monitoring of the operators, to check whether threshold values are exceeded. An example of aerosol monitoring system is the one of type Aer 5000 procured from SARAD GmbH for mobile use as provided in Fig. 20. Such aerosol monitors have a low noise pump, a filter belt for more than 300 filter changes and an ion-implanted silicon detector for α spectrometric differentiation of the radionuclides [35].

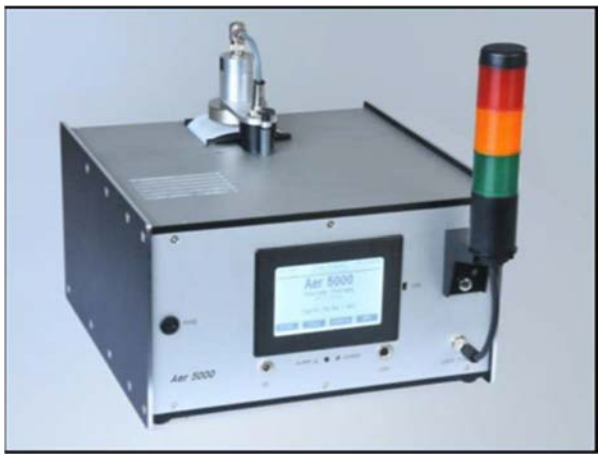

FIG. 20. Aerosol monitoring system used to measure ^{225}Ac presence in the air of laboratory dedicated to [^{225}Ac]Ac-radiopharmaceutical production (courtesy of C. D'Alessandria, TU Munich).

7.6 RADIATION SAFETY FOR OPERATORS DURING ADMINISTRATION OF ^{225}Ac LABELLED RADIOPHARMACEUTICALS

During [^{225}Ac]Ac radiopharmaceutical administration, closed systems that deliver radioactive materials directly into the blood stream should be used. This will limit the risk of contamination events or exposure to staff. Actinium-225 poses a minimal external dose rate and patients can be treated without the need for lead shielding or other radiation limiting interventions. However, care should be taken for contamination risk with absorbent pads to be placed around the injection or infusion area. Proper personal protective equipment such as gloves and laboratory coats should always be worn by all staff involved in the administration of ^{225}Ac containing radiopharmaceuticals [36]. Needle skin pricks and any skin contamination that occur at any time with [^{225}Ac]Ac radiopharmaceutical are considered special events and should be treated promptly and with gravity. The contaminated area should be rapidly cleared and be continuously monitored. In special cases, the monitoring of suspected intake of material should commence [37]. If inhalation is suspected, a bioassay is the preferred method for estimating the amount of material ingested. In this case, a single 24 h biospecimen may be sufficient. For α emitting radionuclides, faecal bioassays are preferred since a larger amount of the radionuclide is excreted through this pathway than compared to the urine [38]. Intake retention functions can be used to estimate the total intake of radioactive material. The cumulative internal dose can be determined as well as the committed effective dose equivalent to the staff member.

7.7 RADIATION SAFETY FOR PATIENTS IN CASE OF EXTRAVASATION DURING ADMINISTRATION OF [^{225}Ac]Ac RADIOPHARMACEUTICALS

Extravasation is a risk to patients undergoing ^{225}Ac labelled radiopharmaceuticals injection, which could lead to serious tissue injury such as tissue necrosis and possible skin carcinoma. Deterministic effects can occur because of therapy administration [39].

Since actions after severe extravasation are very limited, preventive steps should be taken to implement the administration of ^{225}Ac labelled radiopharmaceuticals, such as training of staff and operators, and checking catheters by flushing prior to injection [40]. It is highly recommended to stop any administration if there is any suspicion of extravasation, and the injection site monitored for presence of radioactivity to confirm extravasation [41]. If extravasation occurs, it is recommended to read the paper by van der Pol et al., [42], which gives information about the necessary intervention flowchart to be followed.

7.8 RADIATION SAFETY IN CASE OF PATIENT DEATH

A risk assessment in case of patient death after administration of ^{225}Ac labelled radiopharmaceutical is requested, together with any associated radiation protection control. In case of an event of patient death, the assessment should be immediately made to be able to proceed with body handling, autopsy, embalming, burial, or cremation [43]. During body handling, it is recommended to wear gloves and aprons to prevent contamination due to presence of radioactivity in body fluids and organs [44,45]. The mortuary needs to be declared as a control area, and as such treated by personnel appropriately trained. Consequently, the area and the personnel need to be monitored. All contamination tools used in the area to handle the body need to be stored for monitoring and decontamination or decay storage of radioactive waste. Any waste that has been generated by the body handling and from autopsy should be appropriately handled in agreement with the country's legislation, and records kept. A radiological impact assessment of the burial and crematorium needs to be also carried out within a short interval after handling, and this is subject to national legislation and regulation.

8. FUTURE TRENDS

It is perceived that continuous development and growth will be experienced on all aspects of ^{225}Ac based applications in nuclear medicine. This includes a worldwide effort to increase the amount of ^{225}Ac radionuclide that is produced. Increasing the supply chain of ^{225}Ac will ensure the sustainability of the technology in the nuclear medicine clinics.

Additional chelator development would allow for the radiolabelling of vectors that are sensitive to degradation at the current radiolabelling protocols. This is for example the requirement for DOTA based radiopharmaceuticals to be heated. It is therefore envisioned that more advanced chelator systems could allow for milder labelling protocols. In turn, this could open up multiple possibilities of vectors that currently cannot be utilized due to the restriction to DOTA as chelator for ^{225}Ac.

It is also envisioned that advancements in the field of QC of ^{225}Ac radiopharmaceuticals will be made. To this effort, the IAEA is also supporting research through the CRP on production and QC of ^{225}Ac radiopharmaceuticals (F22075) of which this current document is a part. Partly the focus will also be on the validation of radiochemical purity and the further enhancement of radioanalytical procedures for ^{225}Ac radiopharmaceuticals. The validation of radio-HPLC methods and more real time instant methods of measuring ^{225}Ac would allow for a more accurate determination of radiopharmaceutical stability. The effect of radiolysis and the formation of impurities is a key question that needs further investigation to ensure optimal stability of these radiopharmaceuticals. This also would include feasibility studies towards centralized production of ^{225}Ac radiopharmaceuticals, due to the long physical half-life of ^{225}Ac, it could be shipped further after production. However, to allow this, stability needs to be determined accurately.

Additional investigations towards health physics and the constraints of radiation protection of α emitters in general, but also for ^{225}Ac would be of future interest as more and more facilities start producing these radiopharmaceuticals.

It is also envisioned that as time progress, ^{225}Ac radiopharmaceutical production would move forward towards classical GMP production. The adoption of GMP is however hampered by the unique constraints of ^{225}Ac as a radionuclide, and this transition is not straightforward nor instant, but rather a continuous process of adopting better practices and upgrading technology.

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LIST OF ABBREVIATIONS

cGMP	Current Good Clinical Practice
CRP	Coordinated Research Activity
DOE	Department of Energy United States of America
EU	European Union
HPLC	High Performance Liquid Chromatography
IAEA	International Atomic Energy Agency
IMP	Investigational Medicinal Product
ITLC	Instant Thin Layer Chromatography
QC	Quality Control
TAT	Targeted Alpha Therapy

CHEMICAL ABBREVIATIONS

Ac	Actinum
Bi	Bismuth
DOTA	Dodecane Tetraacetic Acid
DTPA	Diethylenetriamine pentaacetate
PSMA	Prostate Specific Membrane Antigen
Ra	Radium
Th	Thorium

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