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„Radiopharmaceuticals in the European Regulatory Landscape: Impact of Clinical Trial Regulation 536/2014."

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ABSTRACT

Radiopharmaceuticals, unique in their nature and applications, hold significant importance across diverse array of medical disciplines. By leveraging the intrinsic properties of radioactive isotopes, these specialized pharmaceutical compounds have revolutionized medical practices by providing clinicians with powerful tools for non-invasive imaging, targeted therapeutic interventions, and facilitating groundbreaking research initiatives. Nevertheless, their distinct attributes give rise to both specific challenges and opportunities within the European pharmaceutical landscape.

The European pharmaceutical regulatory framework comprises an extensive and intricate network of documents - directives and regulations, creating a system that is both complex and sophisticated. However, as most of these regulations were formulated years ago, they fail to adapt to the dynamic nature of nuclear medicine, and therefore lack recognition of the complexities associated with radiopharmaceuticals. The introduction of Regulation 536/2014 brought promise by initiating various developments, nonetheless, it has also introduced an additional layer of complexity to this regulatory landscape. Therefore, in light of this intricate framework, particularly concerning radiopharmaceuticals, this thesis aims to shed light on how this evolving regulatory landscape influences the development of radiopharmaceuticals, their clinical trials, and eventual integration into healthcare practices, and thereby answering the research question: How does the Clinical Trial Regulation 536/2014 impact radiopharmaceuticals?

Through an in-depth analysis of legal European documents, this thesis scrutinizes the impact of the Regulation 536/2014 on clinical research across the European Union, specifically evaluating its effectiveness in addressing the distinct challenges presented by radiopharmaceuticals. Beyond this, the research extends its focus to other pertinent regulatory documents, such as Directive 2001/83/EC, Commission Directive (EU) 2017/1572 as well as Directive 2001/20/EC, considering their collective influence on shaping the evolving framework for radiopharmaceutical regulation.

ZUSAMMENFASSUNG

Radiopharmazeutika, einzigartig in ihrer Natur und Anwendungen, haben eine signifikante Bedeutung in unterschiedlichsten, medizinischen Disziplinen. Durch die Nutzung der intrinsischen Eigenschaften radioaktiver Isotope haben diese spezifischenpharmazeutischen Verbindungen die medizinische Praxis revolutioniert, indem sie den Klinikerinnen und Klinikern leistungsstarke Werkzeuge für nicht-invasive Bildgebung, gezielte therapeutische Interventionen und bahnbrechende Forschungsinitiativen zur Verfügung stellen. Dennoch führen ihre besonderen Eigenschaften zu spezifischen Herausforderungen als auch Chancen im europäischen pharmazeutischen Umfeld.

Das europäische pharmaeutische Regelwerk umfasst ein umfangreiches und komplexes Netzwerk von Dokumenten - Richtlinien und Verordnungen - und bildet ein System, das gleichermaßen komplex und anspruchsvoll ist. Da jedoch die meisten dieser Regelungen vor Jahren formuliert wurden, könnten sie sich nicht an die dynamische Natur der Nuklearmedizin anpassen und widerspiegeln nicht die Komplexitätenvon Radiopharmazeutika. Die Einführung der Verordnung 536/2014 brachte Hoffnung durch die Initiierung verschiedener Entwicklungen; dennoch führte sie auch eine zusätzliche Ebene von Komplexität in dieses regulatorische Umfeld ein. Daher zielt diese Arbeit angesichts dieses komplexen Rahmens, insbesondere im Zusammenhang mit Radiopharmazeutika, darauf ab, zu beleuchten, wie sich die entwickelnde regulatorische Landschaft auf die Entwicklung von Radiopharmazeutika, ihre klinischen Studien und ihre schließlich Integration in die Gesundheitspraxis auswirkt, und somit die Forschungsfrage zu beantworten: Wie beeinflusst die Clinical Trial Regulation 536/2014 Radiopharmazeutika?

Durch eine eingehende Analyse rechtlicher Dokumente der Europäischen Union untersucht diese Arbeit die Auswirkungen der Verordnung 536/2014 auf die klinische Forschung in der gesamten Europäischen Union. Dabei wird speziell die Wirksamkeit der Verordnung bei der Bewältigung der besonderen Herausforderungen, die sich durch Radiopharmazeutika ergeben, bewertet. Über diese Analyse hinaus richtet die Forschung ihren Fokus auf weitere einschlägige rechtliche Dokumente wie die Richtlinie 2001/83/EG, die Kommissionsrichtlinie (EU) 2017/1572 sowie die Richtlinie 2001/20/EG, um deren kollektiven Einfluss auf die Gestaltung des sich entwickelnden Rahmens für die Regulierung von Radiopharmazeutika zu untersuchen.

Table of content

ABBREVIATIONS

AMP *Auxiliary Medicinal Product*

CTD *Clinical Trial Directive*

CTIS *Clinical Trials Information System*

CTR *Clinical Trial Regulation*

EANM *European Association of Nuclear Medicine*

EMA *European Medicines Agency*

EU *European Union*

FDA *Food and Drug Administration*

GCP *Good Clinical Practice*

GMP *Good Manufacturing Practice*

IAEA *International Atomic Energy Agency*

IMP *Investigational Medicinal Product*

NIMP *Non-Investigational Medicinal Product*

NMEU *Nuclear Medicine Europe*

PET *Positron Emission Tomography*

PIC/S *Pharmaceutical Inspection Co-operation Scheme*

QP *Qualified Person*

SmPC *Summary of Product Characteristics*

SPECT *Single-Photon Emission Computed Tomography*

TABLE OF FIGURES

TABLE OF TABLES

INTRODUCTION

Radiopharmaceuticals represent a pivotal frontier in modern medicine, offering innovative solutions for diagnosis, therapy as well as research across a spectrum of medical disciplines, including oncology, neurology and cardiology. As the medical landscape continues to evolve, the regulation and integration of radiopharmaceuticals into the European Union healthcare framework take on ever-greater significance.(1) With the issue of the new Regulation 536/2014 a lot of things have been set in motion but is it enough? Is their uniqueness adequately reflected?

Radiopharmaceuticals

Radiopharmaceuticals form a unique and dynamic class of medicinal products that combine the principles of nuclear medicine together with pharmaceutical compounds. These agents play a crucial role in modern healthcare by enabling accurate diagnostic imaging and targeted therapy, hence aim to bridge the gap between diagnosis and therapy as well as to contribute to the recently emerging field of personalized medicine. Radiopharmaceuticals are created through the incorporation of radioactive isotopes (radioisotopes) into biologically active molecules in order to allow the visualization of physiological and pathological processes at the molecular level. Radiopharmaceuticals can be classified based on their intended application, the type of radiation emitted, and the imaging or therapeutic modality they utilize, whereby the two main categories include diagnostic and therapeutic radiopharmaceuticals.(2)

Design and Synthesis

The development and synthesis of radiopharmaceuticals is a comprehensive process that demands a high level of expertise in diverse fields, in particular, radiochemistry and pharmaceutical sciences. The process begins with the selection of a radioisotope (radionuclide) based on its decay properties and compatibility with the desired application, which is usually produced in specialized nuclear reactors or cyclotrons. Then, a targeting molecule (carrier) is chosen to deliver the radioisotope to a specific target, such as thyroid gland, brain or cancer cells. These carrier molecules can be represented by small organic compounds, peptides, antibodies, or even nanoparticles. Through radiolabelling techniques, the radioisotope is securely attached to the carrier by a linker (chemical bond linkers, chelators, spacer linkers etc.), ensuring its stability and functionality. As these radiopharmaceuticals have to be produced on demand a precise quality control that verifies the compound's integrity, radiochemical purity, and safety in order to pass the strict registration requirements defined by regulatory agencies is required.(3,4)

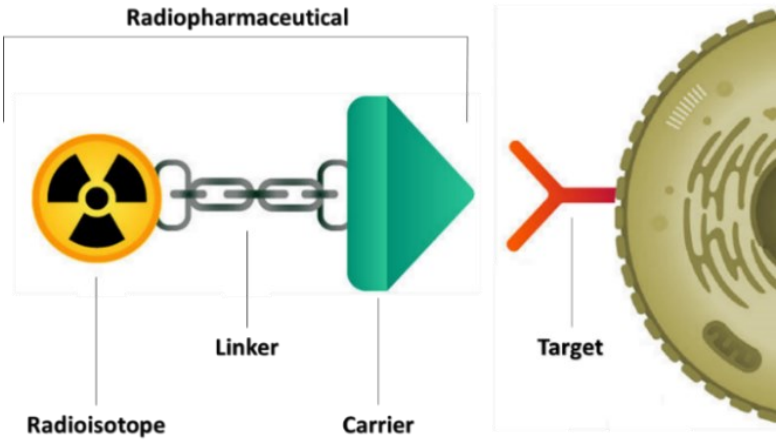

Figure 1: Radiopharmaceutical concept. The radiopharmaceutical consists of a radioactive moiety, a radioisotope, which is connected via linker (chemical bond linkers, chelators, spacer linkers etc.) to the carrier molecule (small organic compounds, peptides, antibodies etc.). The carrier molecule is carefully selected to target specific tissues or cells within the body (targets), in order to facilitate the delivery of the radioisotope to its intended site. Modified from National Cancer Institute.(4)

Mechanism of action

The mechanism and function of radiopharmaceuticals is based on the fundamental principles of nuclear decay and biological targeting. These agents are administered to the patient mostly via intravenous injection, however, other routes of administration such as oral ingestion, or inhalation are possible, depending on the specific characteristics of radiopharmaceuticals and desired outcome. Once in the bloodstream, the radiopharmaceuticals circulate throughout the body until their carrier molecules selectively bind to specific target sites, such as organs, tissues, or pathological areas, where the intended nuclear decay takes place.(5)

Depending on the applicable diagnostic or therapeutic outcome, radionuclides utilize various modes of radioactive decay. In diagnostic applications, radioisotopes emit characteristic radiation in form of gamma rays (γ-rays) or positrons (β+) as they decay. Gamma decay is a nuclear process that occurs when an unstable nucleus transitions from a higher-energy to a lower-energy state, resulting in the release of electromagnetic radiation in the form of highly penetrating gamma rays that can pass through a wide range of body tissues, and thus provide insights into the specific tissue distribution, metabolic activity, and receptor interactions, when detected by specialized imaging techniques, specifically the SPECT (single-photon emission computed tomography), as its principle lies in the detection of the emitted gamma photons by special cameras in order to create 3D images of the radiopharmaceutical's distribution in the body. Another characteristic emission implemented in diagnostic applications – positron decay, is a fundamental process particularly for positron emission tomography (PET) imaging. In this process, an unstable atomic nucleus transforms a proton into a neutron by emitting a positively charged subatomic particle called a positron that subsequently annihilate

with electrons within the body, hence producing pairs of gamma photons traveling in opposite directions. By using specialized PET scanners, time and location of these highly penetrating photon pairs can be recorded, which leads to the construction of highly detailed 3D images of the distribution and activity of the examined radiopharmaceutical in the body.(6,7)

On the contrary, therapeutic radioisotopes exploit the destructive capabilities of ionizing radiation, by utilizing alpha (α) and beta (β-) emissions. During alpha decay, an unstable atomic nucleus emits heavy, positively charged alpha particles, whereby throughout beta decay, high-energy beta particles (electrons or positrons) are emitted. Nevertheless, both of these emissions exhibit moderate to high ionizing power together with limited penetration capabilities as they depose their energy within a short range, varying from few cell diameters to several millimetres into the tissue. These characteristics allow for highly localized and selective delivery of radiation to target cells, where they induce DNA damage, impair cellular functions, hence having the potential to achieve precise therapeutic outcomes, while minimizing harm to surrounding healthy tissues.(8,9)

Diagnostic radiopharmaceuticals

Diagnostic radiopharmaceuticals, the largest and the most evolved group of radiopharmaceuticals, represent a crucial component in the field of nuclear medicine and modern medical imaging. These specific compounds are employed to diagnose a wide range of medical conditions by leveraging the properties of radiation. Those particular radioactive emissions allow for the creation of detailed images when using specialized imaging equipment, such as gamma cameras (SPECT) or PET scanners that reveal specific physiological processes, organ function, or the presence, extent and characteristics of abnormal tissue growth, such as tumours, hence allowing to make accurate diagnoses and informed treatment decisions for the wide array of medical conditions, predominantly in the areas of cardiology, oncology and neurology.(10,11)

Even though diagnostic radiopharmaceuticals expose patients to a small amount of radiation, the doses are generally considered safe, as the radiation amount is kept as low as reasonably achievable and stringent safety regulations and guidelines are followed. Also, due to their biochemical function or targeted delivery, they tend to accumulate only in the investigated organs and tissues, thus causing no harm to other parts of the body. In addition, the diagnostic radioisotopes usually indicate short half-lives (minutes to hours) so that the radiation exposure remains as low as possible, hence the benefits of obtaining important diagnostic information outweigh the risks associated with radiation exposure.(12)

The choice of the diagnostic radiopharmaceutical and imaging technique depends on the medical condition being investigated.(13) Summary of the common diagnostic radioisotopes with their physical properties, common radiopharmaceutical and clinical applications can be seen in Table 1.

Radioisotope	Half-life	Mode of decay	Major application	Common radiopharmaceutical forms with their clinical applications
Technetium-99m ^{99m}**Tc**	6.0 h	γ	SPECT	**[^{99m}Tc]pertechnetate** – Imaging of thyroid, salivary gland, and urinary bladder **[^{99m}Tc]sestamibi** – Cardiac perfusion imaging **[^{99m}Tc]Technetium sulfur colloid** – Imaging of liver, spleen, and bone marrow
Indium-111 ^{111}**In**	67.2 h	γ	SPECT	**[^{111}In]oxyquinoline** – Imaging and detection of inflammatory processes **[^{111}In]pentetreotide** – Imaging of neuroendocrine tumours **[^{111}In]pentetate** – Brain imaging
Iodine-123 ^{123}**I**	13.2 h	γ	SPECT	**[^{123}I]sodium iodide** – Imaging of thyroid gland and its malignancies **[^{123}I]ioflupane** – Brain imaging **[^{123}I]iobenguane** – Imaging of neuroendocrine tumours, cardiac imaging
Fluorine-18 ^{18}**F**	1.8 h	β^+	PET	**[^{18}F]fluorodeoxyglucose** – Imaging of glucose metabolism in oncology **[^{18}F]florbetapir** – Brain imaging (detection of Alheimer's disease) **[^{18}F]fluoroestradiol** – Imaging of metastatic breast cancer
Gallium-68 ^{68}**Ga**	1.1 h	β^+	PET	**[^{68}Ga]Ga-DOTATOC** – PET Imaging of neuroendocrine tumours **[^{68}Ga]Ga-DOTATATE** – PET Imaging of neuroendocrine tumours **[^{68}Ga]Ga-PSMA-11** and **[^{68}Ga]Ga-PSMA-617** – Imaging of prostate cancer

Table 1: Summary of common diagnostic radioisotopes, half-life, decay mode and application as diagnostic radiopharmaceutical.(10,11,13)

In essence, diagnostic radiopharmaceuticals have revolutionized the medicine's practice by providing non-invasive, highly sensitive tools for diagnosing and monitoring various biological functions and medical conditions. Their ability to reveal detailed information about the body's internal processes has improved patient care and treatment outcomes across a broad spectrum of diseases and disorders.

Therapeutic radiopharmaceuticals

Therapeutic radiopharmaceuticals represent a rapidly evolving branch of nuclear medicine as they combine the precision of molecular targeting together with the potent therapeutic effects of radiation, hence enabling treatment of various medical conditions by destroying or controlling diseases at cellular and molecular levels. These agents are designed to precisely deliver radiation directly to specific disease sites. This precision is achieved through the integration of radioactive isotopes into carrier molecules or ligands that can selectively bind to target cells or within tumours of interest. Once administered to the patient, these radiopharmaceuticals accumulate at the disease site, where the emitted radiation (either beta particles or alpha particles) damages or destroys the targeted cells and the cells in the surrounding. These emissions indicate short ranges, hence allowing local exposure, while minimizing damage to healthy tissues, thus making therapeutic radiopharmaceuticals an important player in the treatment of cancer.(10,14,15)

Although, therapeutic radiopharmaceuticals indicate a diverse array of applications, oncological diseases remain their primary focus, as they possess numerous advantages over traditional cancer therapies, including surgery, chemotherapy, and external beam radiation therapy. These compounds are engineered to specifically target cancer cells, thereby resulting in shorter treatment durations and low long-term toxicity, hence sparing healthy tissues, and minimizing side effects. Moreover, they enable a personalized approach to cancer treatment, as they can be tailored to a patient's specific tumour characteristics, and due to their simple intravenous application, complex surgeries can be avoided. However, their greatest potential lies in targeting both primary and metastatic disease sites, that may be challenging to access with other treatments, while also in their ability to overcome various mechanisms of drug resistance frequently encountered in conventional chemotherapy.(16,17)

Numerous noteworthy therapeutic radioisotopes and thus the corresponding radiopharmaceuticals are now being routinely used in the treatment of different medical conditions, see Table 2.

Radioisotope	Half-life	Mode of decay	Common radiopharmaceutical forms with their clinical applications
Iodine-131 ^{131}**I**	8 d	β^-	**[^{131}I]human serum albumin** – Radioimmunotherapy **[^{131}I]iobenguane** – Treatment of neuroendocrine tumours **[^{131}I]sodium iodide** – Treatment of thyroid disorders and malignancies
Lutetium-177 ^{177}**Lu**	6.7 d	β^-	**[^{177}Lu]Lu-DOTATATE** – Treatment of neuroendocrine tumours (Lutathera®) **[^{177}Lu]vipivotide tetraxetan** – Treatment of metastatic prostate cancer (Pluvicto®)
Yttrium-90 ^{90}**Y**	2.7 d	β^-	**[^{90}Y]Yttriumchloride** – Treatment of inoperable cancers **[^{90}Y]ibritumomab tiuxetan** – Treatment of non-Hodgkin's lymphoma
Radium-223 ^{223}**Ra**	11.4 d	α	**[^{223}Ra]Radiumdichloride** – Treatment of prostate cancer and bone metastasis
Strontium-89 ^{89}**Sr**	50.5 d	β^-	**[^{89}Sr]chloride** – Treatment of bone metastasis

Table 2: Summary of common therapeutic radioisotopes, half-life, decay mode and their application as therapeutic radiopharmaceutical.(10,17)

Overall, therapeutic radiopharmaceuticals hold great promise for cancer therapy as well as for the treatment of other medical conditions as they offer more effective, personalized and less invasive therapeutic options with reduced side effects. Furthermore, they remain in the focus of intensive research and development, with ongoing efforts to expand their applications, enhance targeting strategies, and improve patient outcomes.

Theranostic radiopharmaceuticals

Theranostic radiopharmaceuticals are a specialized class of radiopharmaceuticals that serve both diagnostic and therapeutic purposes to access the same biological processes. The term "theranostic" is a combination of "therapy" and "diagnostic," highlighting the dual purpose of these agents. In most of the cases, the targeting moiety – often a small peptide – stays the same, whereas the linker and chelator are changed dependent on the purpose (Figure 1). Whereby the diagnostic part typically consists of a radioactive isotope that emits radiation suitable for imaging and diagnosis, the therapeutic component contains a different radioactive isotope or a higher dose of the same isotope that can deliver radiation to the specific disease site in order to selectively damage or destroy the target cells, thus contribute to the treatment of the disease. Nevertheless, these theranostic radiopharmaceuticals are designed to seamlessly integrate both diagnosis and therapy in order to deliver highly targeted, personalized treatments as they enable precise therapy by minimizing damage to healthy tissues and reducing side effects compared to conventional radiation therapy or chemotherapy. In addition, this approach can be tailored to the patient's specific condition, as the diagnostic component helps to identify suitable candidates for the therapy as well as provides ad hoc information on treatment response. While cancer treatment remains a primary focus, theranostic radiopharmaceuticals are now being explored for wide range of other diseases, including neurodegenerative disorders (e.g., Parkinson and Alzheimer's disease), cardiovascular conditions as well as autoimmune disorders.(18,19) One of the most important theranostic pairs, two radioisotopes where one can be used for diagnosis and the other for treatment, currently in clinics are gallium-68 for diagnosis and lutetium-177 for therapy.

Several notable theranostic radiopharmaceuticals are currently employed in clinical practice, while many others exhibit significant potential in ongoing clinical trials.(20,21) One well-known example is [^{177}Lu]DOTATATE in combination with [^{68}Ga]DOTATATE or [^{68}Ga]DOTATOC as imaging agents, used as a first choice in the treatment of neuroendocrine tumours. Notably, this therapeutic radiopharmaceutical, marketed as Lutathera® (see Figure 2A), was the first to obtain approvals from both the European Medicines Agency (EMA) on September 26, 2017, and the U.S. Food and Drug Administration (FDA) on January 26, 2018.(22) [^{177}Lu]vipivotide tetraxetan (available under the trade name Pluvicto® - see Figure 2B) together with [^{68}Ga]PSMA as diagnostic agent, present another theranostic or radiopharmaceuticals that received approval by FDA (March 23, 2022) as well as EMA (December 09, 2022) for the treatment of adult patients with metastatic castration-resistant prostate cancer.(22–25)

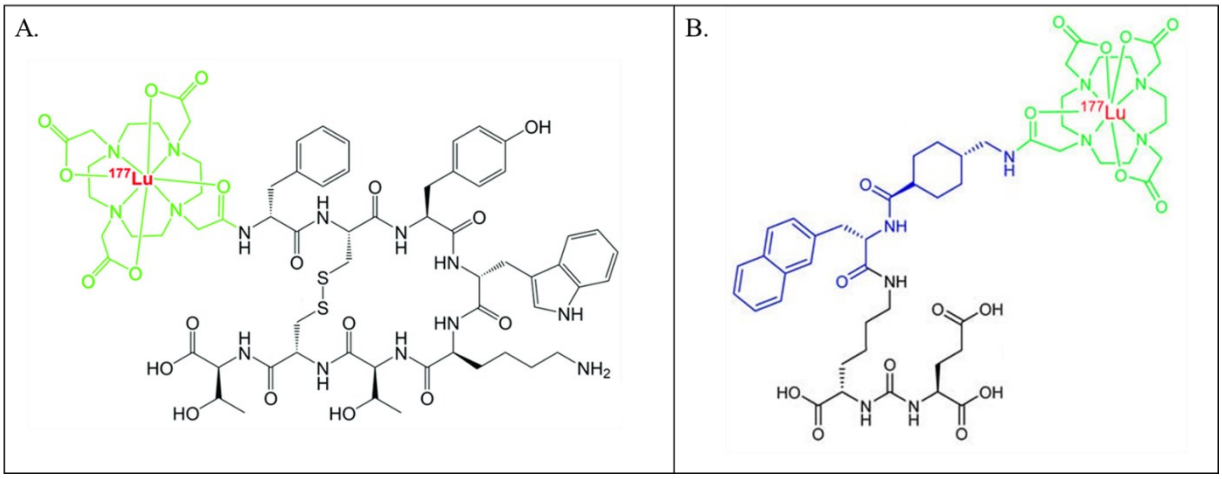

Figure 2: Structures of therapeutic parts of approved theranostic radiopharmaceuticals. A. Chemical structure of [^{177}Lu]DOTATATE, available as Lutathera®. The structure consists of a radioisotope [^{177}Lu] (depicted red) inside the DOTA chelating moiety (depicted green) which is connected to carrier molecule – Octreotate (depicted black). **B.** Chemical structure of [^{177}Lu]vipivotide tetraxetan, available as Pluvicto®. The structure consists of a radioisotope [^{177}Lu] (depicted red) inside the DOTA chelating moiety (depicted green) which is connected via linker (containing amino acid 2-naphthyl-L-alanine as well as tranexamic acid – depicted blue) to carrier molecule that encompasses the typical PSMA-binding motif Glu-NH-CO-NH-Lys (depicted black).(22,25)

Furthermore, other prominent theranostic pairs, e.g. iodine-based (iodine-123 and iodine-131) as well as yttrium (yttrium-89 and yttrium-90) and indium/actinium (indium-111 and actinium-225) have also demonstrated their efficacy in different combinations with targeting moiety as theranostics in the treatment of a diverse array of severe diagnoses, see Table 3.

Disease	Target	Diagnostic agent	Therapeutic agent
Thyroid cancer and hyperthyroidism	Sodium/iodide symporter (NIS)	**[^{123}I]sodium iodide**	**[^{131}I]sodium iodide**
Neuroendocrine tumours – neuroblastoma pheochromocytomas paragangliomas	Norepinephrine transporter (NET)	**[^{123}I]iobenguane**	**[^{131}I]iobenguane**
Neuroendocrine tumours – gastroenteropancreatic tumour	Somatostatin receptor (SSTR)	**[^{68}Ga]DOTATOC** **[^{68}Ga]DOTATATE**	**[^{177}Lu]DOTATATE** **[^{177}Lu]DOTATOC** **[^{90}Y]DOTATATE** **[^{90}Y]DOTATOC** **[^{225}Ac]DOTATATE** **[^{225}Ac]DOTATOC**
Metastatic prostate cancer	Prostate-specific membrane antigen (PSMA)	**[^{68}Ga]PSMA-11** **[^{68}Ga]PSMA-617**	**[^{177}Lu]vipivotide tetraxetan** **[^{225}Ac]PSMA-617**
Breast, ovarian and gastric cancer	Receptor tyrosine-protein kinase erbB-2 (HER2)	**[^{89}Zr]trastuzumab**	**[^{177}Lu]trastuzumab** and derivatives

Table 3: Examples of theranostics of radiopharmaceuticals, including their target, diagnostic and therapeutic part.(20,21)

Ultimately, these theranostic radiopharmaceuticals represent the integration of diagnostic and therapeutic components to provide precision medicine, improve disease characterization, and optimize targeted therapy while minimizing side effects, particularly in cancer treatment. However, the field is dynamic, hence ongoing research and clinical trials continue to explore new theranostic agents and expand their applications to additional medical conditions.

Radiopharmaceuticals versus Pharmaceuticals

Even though, radiopharmaceuticals and pharmaceuticals are both classified as medicinal products, hence must fulfil the same regulatory requirements, there are significant differences present between them. They serve different purposes, have distinct characteristics, and differ in terms of their composition, purpose, mechanisms of action, production, and intended outcomes.(26) The key differences between radiopharmaceuticals and therapeutic drugs can be seen in Table 4.

	Radiopharmaceuticals	Pharmaceuticals
Composition	Targeting molecule labelled with radioisotope (radioactive)	Pharmacologically active compounds (non-radioactive)
Purpose	Diagnostic and therapeutical purposes possible	Therapeutical purposes
Application	Mostly intravenous application	Different routes of application
Administration	Administration only in hospitals	Administration dependent on purpose
Dosing	Microdosing concept (no biological response wanted)	Pharmacological dose (to achieve biological response)
Production	On demand production (short shelf-life product)	Batch production (long shelf-life product)
Safety concerns	Radiation safety requirements (as low as reasonably achievable)	High safety requirements

Table 4: Summary of differences between radiopharmaceuticals and pharmaceuticals.(26)

In summary, radiopharmaceuticals are significantly distinct from conventional pharmaceuticals, as they contain radioactive isotopes bound to carrier molecules, and hence function through radiation emissions for diagnostic imaging or targeted therapy, whereby pharmaceuticals have to unfold a biological relevant process within the patient's body to unfold their purpose. Due to their radioactive character, radiopharmaceuticals require a small-scale/on demand production in specialized facilities, hospital administration (intravenous), and precise dosing (measured in microcuries or becquerels) with stringent radiation safety protocols. On the contrary, pharmaceuticals encompass diverse medications,

have various routes of administration, and are used for therapeutic purposes with dosing based on patient factors, emphasizing different safety considerations such as side effects and drug interactions.

European Union

The European Union (EU) is a political and economic union comprised of 27 European countries, founded with the aim of promoting peace, stability, and prosperity in Europe after World War II. Over the years, it has evolved into unique supranational organization with a wide range of competencies, characterized by single market, shared policies, and a web of institutions. At its core, the EU has pursued several primary objectives including economic integration, political cooperation, and the preservation of peace that help to balance national sovereignty with collaborative decision-making processes among the member states. Its governance structure encompasses institutions like the European Commission, European Parliament, and Council of the EU that all collaborate to create shared policies and laws. Even when facing different challenges, EU remains a crucial player on the global stage due to its ability to promptly adapt and address contemporary issues, not to exclude those in healthcare.(27,28)

European Union structure in the radiopharmaceutical context

The structure of the EU is characterized by a multi-tiered system of institutions and decision-making processes. It involves several bodies that work together in order to formulate policies, pass legislation, and ensure the implementation of EU laws, whereby many of these institutions play crucial roles also in regulating radiopharmaceuticals, hence ensuring their safe and effective use within the EU. These key institutions include: European Commission, European Parliament, Council of the European Union, European Medicines Agency (EMA) and National Competent Authorities.(29)

The European Commission is responsible for proposing and implementing EU policies, among others directives and regulations. These are particularly important in the context of radiopharmaceuticals, as they directly regulate the radiopharmaceutical‘s regulatory and marketing authorization processes, leading to their safety and quality assurance. As the legislative body of the EU that participates in shaping of the EU‘s legislation and adopting the European Commission’s proposals, European Parliament, together with Council of the EU that represents the national governments of EU member states, are both in charge of drafting and embracing the legislation that impacts the use of radiopharmaceuticals within the EU. The European Medicines Agency (EMA), a decentralized institution of the EU, is in control of assessing and supervising medicinal products in EU, hence evaluates the safety, efficacy, and quality of radiopharmaceuticals. Furthermore, EMA also provides scientific opinions for the regulatory approvals and marketing authorization processes in the respective member states. In addition, each EU member state has designated National Competent Authorities that are responsible for ensuring compliance with different EU regulations, as well as providing support at the national level. Regarding radiopharmaceuticals, they play a vital role in assessing and granting marketing authorizations as well as ensure compliance with manufacturing standards. Close cooperation

between all these institutions is essential in order to bring newly developed radiopharmaceuticals into clinical trials and later to the market, while at the same time ensuring their safe and effective use within the EU.(30,31)

European radiopharmaceutical regulatory framework

The European radiopharmaceutical regulatory framework is mainly defined by the EU's legislative power that is manifested through the deployment of two primary legal instruments: directives and regulations. Directives are legally binding acts issued by the EU institutions, in particular the European Commission that set out specific goals all member states must achieve within a specified timeframe. Nevertheless, these directives provide member states with a certain degree of flexibility in the implementation of required measures, hence allowing them accommodation of national variations. The directive process begins with the proposal initiated by the European Commission. Afterwards, the European Parliament together with the Council of the EU take the charge by reviewing, amending, and, conclusively, adopting the proposal. Once approved, member states must transpose the directive into their national laws, while considering their specific legal and administrative systems. In the radiopharmaceutical context, directives, specifically the Directive 2001/83/EC, Directive 2001/20/EC and Commission Directive (EU) 2017/1572 (replaced the Directive 2003/94/EC) establish common quality and safety standards, define procedures for marketing authorization, and outline requirements for their safe handling.(32–34)

Regulations present another important key instrument of the EU‘s law. Unlike directives, regulations, have direct effect and are immediately applicable across all member states, without the need for national transposition, and therefore are typically implemented when there is a need for uniform rules and standards across various areas within the EU. The regulation process includes proposal drawn up by the European Commission, followed by review, amendment, and adoption of the proposal by the European Parliament together with the Council of the EU. This leads to immediate enforceability in all member states upon adoption. In relation to radiopharmaceuticals, regulations, in particular Regulation 536/2014, holds significant importance as it clarifies and unifies the rules formerly outlined in Directive 2001/20/EC, while also addressing emerging concerns such as manufacturing, labelling, packaging, and pharmacovigilance.(33,35)

In addition to directives and regulations governing medicinal products within the EU, the Council of Europe establishes the legally binding framework known as the European Pharmacopoeia that sets specifications for purity, quality, and testing methods in order to ensure the safety and efficacy of medicines including radiopharmaceuticals. Moreover, the radiopharmaceutical regulatory framework is also supported by various legally non-binding guidelines and guidance documents published by different organisations and associations such as EMA, European Association of Nuclear Medicine (EANM), International Atomic Energy Agency (IAEA) or Pharmaceutical Inspection Co-operation

Scheme (PIC/S) with the aim to provide scientific opinions for the development and production of radiopharmaceuticals along with the support by the implementation and understanding of EU's directives and regulations. (36)

Directive 2001/83/EC

Directive 2001/83/EC, enacted on November 6, 2001, with current consolidated version dated January 1, 2022, represents a significant milestone in shaping the regulatory landscape for medicinal products intended for human use within the EU. This Directive marked one of the earliest initiatives reflecting the EU's dedication to safeguard public health, foster pharmaceutical innovation, and ensure the availability of safe and effective medicines. Some of its main elements include the establishment of marketing authorization procedures followed by uniform evaluation process, the classification of medicines into prescription and non-prescription categories, inclusion of comprehensive pharmacovigilance requirements for monitoring of adverse drug reactions, enhancement of the quality and manufacturing standards, unification of packaging and labelling requirements, introduction of data and market exclusivity to protect data submitted during the authorization process and confer exclusive marketing rights for a defined period, as well as extension of the regulatory oversight to homeopathic and herbal medicinal products. In the radiopharmaceutical context, this Directive provides an overview of the key aspects essential for radiopharmaceutical manufacturers to meet regulatory requirements, protect patient safety, and facilitate innovation in this specialized field of medicine.(37,38)

Directive 2003/94/EC and Commission Directive (EU) 2017/1572

Directive 2003/94/EC, in force from October 8, 2003, till January 31, 2022, adopted as a part of the EU's ongoing efforts to harmonize pharmaceutical regulations across member states, was designed to enhance the quality of medicinal products intended for human use by establishing consistent Good Manufacturing Practice (GMP) standards for their manufacturing, packaging, labelling, and distribution. Among the key aspects belong the establishment of comprehensive quality management systems, manufacturing authorizations, oversight by Qualified Persons (QPs) responsible for product release, rigorous inspections, stringent record-keeping, stability testing, and mutual recognition of GMP standards between EU member states with the aim to ensure the consistent quality and safety of medicinal products and thereby facilitating their free movement within the EU.(39,40) However, as there was an urgent need to separate the manufacturing requirements for medicinal products for human use and investigational medicinal products for human use, this Directive was repealed and correspondingly replaced by the Commission Directive (EU) 2017/1572. Nevertheless, this new EU GMP Directive retains similar structure as the old directive and the majority of the requirements remains unchanged. Regarding radiopharmaceuticals, Directive 2003/94/EC as well as Commission Directive (EU) 2017/1572 set out just fundamental principles for the GMP of radiopharmaceuticals, whereby not taking

into account their unique characteristics and safety aspects, hence regulatory agencies and institutions (EMA, EANM, IAEA) often provide specific guidelines to deal with these challenges.(41,42)

Directive 2001/20/EC

Directive 2001/20/EC, referred to as the Clinical Trial Directive (CTD), presented a pivotal legislative instrument within the EU by holding significant implications for the conduct of clinical trials involving medicinal products for human use. In force from April 2001 until its repeal on January 31, 2022, this Directive emerged as a product of a complex historical development and a concerted effort to address critical challenges in the regulation and conduct of clinical research across EU member states. One of the primary motivations was the recognition of the necessity to ensure a high level of protection for trial subjects, harmonization of ethical standards, and facilitation of free movement of medicinal products for clinical trial purposes within the EU as well as the outline of general rules for the conduct of clinical trials, hence the key provisions included the requirement for the prior authorization of clinical trials, the pivotal role of ethics committees in evaluating trial protocols, the imperative to obtain informed consent from trial subjects, and the robust reporting mechanisms for adverse events. In addition, this Directive placed explicit responsibilities on sponsors, clinical researchers, and competent authorities, while emphasizing adherence to the principles of Good Clinical Practice (GCP) for the design, conduct, monitoring, auditing, recording, analysis, and reporting of clinical trials. However, given its nature, this Directive required transposition into national legislation, which has led to variations in the interpretation and application of the Directive across member states. Moreover, This Directive covered only clinical trials conducted with medicinal products for human use, encompassing various therapeutic indications, whereby not including non-interventional trials (clinical studies other than clinical trials or studies not fulfilling any of the conditions defining a clinical trial) or trials of medical devices. Nevertheless, the main burden was represented by the decentralized regulatory oversight, with each EU member state being responsible for supervising clinical trials through their respective National Authorities and Ethics Committees, hence leading to disparate practices and procedures, impacting the efficiency and consistency of clinical research. As a result, clinical trial sponsors had to navigate complex and distinct application processes in each member state where they intended to conduct the trial, whereby considering country-specific deadlines and communication styles. Besides, informed consent, a crucial element of clinical research, was subject to the differing requirements of national regulations, which added another layer of complexity and led to further disparities. Given that this Directive primarily provided only a general overview of the regulation of the clinical research across the EU, radiopharmaceuticals under investigation in clinical trials were in principle subject to the same regulatory principles set out in the Directive 2001/20/EC.(43,44)

Regulation 536/2014

Regulation 536/2014, also known as the Clinical Trial Regulation (CTR), represent a comprehensive legislative framework established by the EU with the aim to streamline and harmonize conduct of clinical trials across Member States as well as to provide an appropriate solution to the limitations of the outdated Directive 2001/20/EC, by enhancing safety and efficiency of clinical research, and fostering innovation in the development of new medicinal products as this Regulation covers clinical trials with Investigational Medicinal Products (IMPs) for human use, encompassing all kind of clinical trials as well as studies, while also being applicable to non-interventional trials and trials of medical devices. While officially enacted on April 16, 2014, the implementation of Regulation 536/2014 was realized on January 31, 2022, whereby this delay was necessary in order to ensure the establishment of an electronic centralized EU portal and database for clinical trial applications (CTIS - Clinical Trials Information System), and so provide a coordinated approach to trial oversight, by streamlining the procedures and promoting consistency in standards and practices and introducing a centralized approval process for multinational clinical trials by simplifying procedures for sponsors seeking to conduct studies in multiple EU countries through the joint EU CTIS as it establishes the EMA as the main point for the assessment and approval of applications, ensuring consistent evaluation criteria and reducing duplicative efforts. To enhance the safety, the Regulation outlines new stringent requirements for informed consent processes, as well as establishes robust safety monitoring mechanisms that emphasize on-time reporting of safety issues as sponsors are required to provide regular safety updates, with EMA coordinating safety assessments and so contributing to a comprehensive understanding of a trial's risk-benefit profile. In addition, the regulation places a strong emphasis on transparency, promoting public access to information related to clinical trials by making the outcomes and results of the trials publicly available and so enhancing the dissemination of knowledge and accountability. In the realm of radiopharmaceuticals, Regulation 536/2014 makes a significant impact, marking a pioneering effort in acknowledging and addressing their unique characteristics. By permitting special exemptions (e.g. GMP, marketing authorization) this regulation not only recognizes the distinct nature of radiopharmaceuticals but so actively promotes the advancement of clinical research within this unique field.(45–47)

Directive 2001/20/EC versus Regulation 536/2014

Ultimately, Regulation 536/2014 represents a transformative shift in the regulation of clinical trials towards a more unified, streamlined, and patient-centric approach within the EU. It strives for harmonization, efficiency, transparency, as well as enhanced patient protection. By transitioning from a Directive to a Regulation and introducing centralized processes, it addresses many of the complexities and disparities associated with the previous regulatory framework, providing a more robust and patient-focused system for the organization and conduct of clinical trials. An overview of the general comparison between the Directive 2001/20/EC and Regulation (EU) 536/2014 can be seen in Table 5.

Directive 2001/20/EC	Regulation 536/2014
Need for implementation by each member state through national legislation	**Directly applicable** to all member states
Definition of clinical trial	Adapted definition of clinical trial, non-interventional study, low-intervention trial
No harmonized "tool" for the conduct of clinical trials	Easier conduct of clinical trials via electronic **Clinical Trials Information System - CTIS**
Fragmented submission process → Separate application to National Authorities + Ethics Committees in each Member State	**Simplified submission process →** Single decision per member state (National Authority + Ethics Committee) based on one single electronic submission (favours collaboration between member states)
Country-specific timelines and deadlines & Country-specific communication methods	**Harmonized → via CTIS**
Individual assessment and Safety reporting by each member state	**Facilitated assessment and Safety reporting** of clinical trials with one reporting member state
High standards of safety for the protection of patients	Strengthened standards of safety for the protection of patients (Informed Consent Form)
Limited transparency and data available to the public	**Improved transparency and public data** availability

Table 5: Summary of differences between Directive 2001/20/EC and Regulation 536/2014.(44,47)

Conduct of clinical trial in accordance with Directive 2001/20/EC and Regulation 536/2014

Even though specific requirements and procedures differ between Directive 2001/20/EC and Regulation 536/2014, the underlying principles for the general conduct of clinical trials remain consistent. As outlined in both documents, the clinical trial process starts with the formation of detailed clinical trial protocol by sponsor (an individual or company responsible for the conduct and financing of the clinical trial) that outlines the objectives, design, methodology, and ethical considerations of the trial. Subsequently, the protocol must be submitted to the relevant ethics committees as well as competent authorities, which review the protocol and asses the suitability of the clinical researchers, facilities, and informed consent procedures, in order to obtain approval for the conduct of the trial. Additionally, before the initiation of the trial, the sponsor must ensure that manufacturing, import, and quality control of the IMP (pharmaceutical substance being investigated in clinical trials to assess its safety and efficacy before potential regulatory approval and market availability) as well as Auxiliary Medicinal Product (AMP - medicinal product utilized for the requirements defined in the clinical trial protocol, distinct from its role as an IMP; sometimes also referred to as NIMP - Non-Investigational Medicinal Product) comply with the requirements (e.g. GMP) defined in the respective legal acts. After acquiring all required approvals, clinical trial sites, including hospitals or research centres, are selected and initiated, whereby recruited participants, meeting the inclusion criteria for the trial, are provided

with detailed information about the trial, including its purpose, procedures, potential risks, and benefits as the informed consent must be obtained from each participant voluntarily before their enrolment in the trial. Once a clinical trial has commenced, the overall conduct of the trial must be strictly monitored and adhere to the principle of GCP, hence all data generated during the trial must be collected and recorded as per the protocol and comprehensive records must be maintained, with all adverse events reported immediately to the regulatory authorities. After concluding the trial, the sponsor is required to present a conclusive report to both the competent authority and ethics committee as these entities hold the ultimate decision-making authority regarding the granting of marketing authorization for the investigated medicinal product.(44,47,48)

METHODS

The methodology for this master thesis involved conducting an analysis of legal EU documents together with an extensive literature research, whereby specific keywords were utilized as the primary search criteria.

The literature research was performed by reviewing websites and publishers' sites for articles, reports, and documents about radiopharmaceuticals within their European regulatory framework. The credibility of the identified articles and publications was assessed based on specific criteria, including the number of citations, the publication source, and the publication year, all of which were considered to ensure their relevance. A significant portion of the findings originated directly from the official websites of authoritative sources, namely the International Atomic Energy Agency, European Association of Nuclear Medicine, EU, and the European Medicines Agency. In addition, general search engines such as google scholar and google were used.

Selected keywords were incorporated in this literature search (independently as well as in various combinations): radiopharmaceutical, radiopharmaceuticals, nuclear pharmacy, nuclear medicine, radiobiology, diagnostic radiopharmaceutical, therapeutic radiopharmaceutical, theranostic radiopharmaceutical, theranostics, radionuclide imaging, radionuclide therapy, European Union, European Commission, European Parliament, Council of the European Union, EMA, National competent authorities (human), directive, regulation, regulatory framework, Directive 2001/83/EC, Directive 2003/94/EC, Commission Directive (EU) 2017/1572, Directive 2001/20/EC, Regulation 536/2014, European Pharmacopoeia; and the Directive 2001/83/EC, Directive 2003/94/EC, Commission Directive (EU) 2017/1572, Directive 2001/20/EC, as well as Regulation 536/2014 were thoroughly reviewed, analysed and compared, mainly in regard to radiopharmaceuticals.

RESULTS

Directive 2001/83/EC in the radiopharmaceutical context

Directive 2001/83/EC, a foundation of the European pharmaceutical regulatory framework, contains only limited information in relation to radiopharmaceuticals. Specific provisions addressing this distinctive class of medicinal products can be found in Articles 1, 3, 4, 6, 7, 11, 63, 66, 67, and 83, as well as Annex I. The respective Articles will be shown and discussed in detail in the following paragraphs.

Article 1

Article 1 provides definitions pertinent to this Directive, while specifically outlining four crucial terms associated with radiopharmaceuticals:

For the purposes of this Directive, the following terms shall bear the following meanings:

[...]

6. Radiopharmaceutical:

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

7. Radionuclide generator:

Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

8. Radionuclide kit:

Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

9. Radionuclide precursor:

Any other radionuclide produced for the radio-labelling of another substance prior to administration.(38)

However, apart from these definitions, which remained unchanged since the adoption of the Directive, there are only few supplementary sources of information exclusively dedicated to radiopharmaceuticals within this document.

Article 3

The explanation of the scope along with specific exemptions for magistral and official formulas, as well as for the radionuclides in form of sealed sources is outlined in the Article 3:

This Directive shall not apply to:

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).

2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the official formula).

[…]

5. Any radionuclides in the form of sealed sources.(38)

This designation as a magistral or official formula could be also extended to radiopharmaceuticals, given that they are usually prepared on demand in hospital pharmacies to directly meet the specific needs of individual patients.

Article 4

Obligation to radiation protection for patients undergoing medical examination or treatment, medical workers as well as for the general public is defined in the Article 4:

1. Nothing in this Directive shall in any way derogate from the Community rules for the radiation protection of persons undergoing medical examination or treatment, or from the Community rules laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation.(38)

Notwithstanding, member states retain the authority to designate specific entities for such protection, whereby this flexibility does not preclude member states from implementing more stringent rules, which, however, lead to variations in radiation protection standards across different countries.

Article 6 and 7

Articles 6 and 7 are dedicated to marketing authorization requirements. According to Article 6, marketing authorization is required for all radionuclide generators, radionuclide kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals:

1. No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.

2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, radionuclide kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.(38)

However, as stated in the Article 7, no marketing authorization is necessary for radiopharmaceuticals prepared immediately prior to use, provided that it has been prepared by a person, or an establishment authorized, within an approved medical facility in accordance with the manufacturer's instructions (extemporaneous preparation):

A marketing authorization shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, radionuclide kits or radionuclide precursors in accordance with the manufacturer's instructions.(38)

Nevertheless, this provision grants member states the authority to designate specific entities for the extemporaneous preparation of radiopharmaceuticals.

Articles 11, 63, 66 and 67

The provisions of Articles 11, 63, 66 and 67 are designated to the Summary of Product Characteristics (SmPC), labelling of outer packaging and immediate packaging as well as patient information leaflet, and whereby Articles 11, 66 and 67 specify additional requirements beyond those applicable to conventional medicinal products…

Article 11

The summary of the product characteristics shall contain the following information:

[…]

8. For radiopharmaceuticals, full details of internal radiation dosimetry.

9. For radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

Article 66

1. The outer carton and the container of medicinal products containing radionuclides shall be labelled in accordance with the regulations for the safe transport of radioactive materials laid down by the International Atomic Energy Agency. Moreover, the labelling shall comply with the provisions set out in paragraphs 2 and 3.

2. The label on the shielding shall include the particulars mentioned in Article 54. In addition, the labelling on the shielding shall explain in full, the codings used on the vial and shall indicate, where necessary, for a given time and date, the amount of radioactivity per dose or per vial and the number of capsules, or, for liquids, the number of millilitres in the container.

3. The vial shall be labelled with the following information: the name or code of the medicinal product, including the name or chemical symbol of the radionuclide; the batch identification and expiry date; the international symbol for radioactivity; the name of the manufacturer; the amount of radioactivity as specified in paragraph 2.

Article 67

The competent authority shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, radionuclide generators, radionuclide kits or radionuclide precursors. The text of this leaflet shall be established in accordance with the provisions of Article 59. In addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the medicinal product and special precautions for the disposal of the packaging and its unused contents.(38)

Article 63 allow some exemptions from labelling of outer packaging and immediate packaging and package leaflet if the product is not intended for self-administration, hence applicable for all radiopharmaceuticals:

[…]

3. The competent authorities may exempt labels and package leaflets for specific medicinal products from the obligation that certain particulars shall appear and that the leaflet must be in the official language or languages of the Member State where the product is placed on the market, when the product is not intended to be delivered to the patient for self-administration.(38)

Article 83

In addition, Article 83 introduces the possibility for member states to apply more stringent requirements in the regulation of the distribution of radiopharmaceuticals as it diverges from the distribution of conventional medicinal products:

The provisions of this Title shall not prevent the application of more stringent requirements laid down by Member States in respect of the wholesale distribution of: […] – radiopharmaceuticals.(38)

Last provisions requiring additional information for radiopharmaceuticals in the Directive are to be found in the Annex I of the Directive, dedicated to the requirements for the dossier in relation to chemical-, biological-, pharmaceutical-, toxicological- and pharmacological tests of the medicinal product and clinical documentation.

A comprehensive summary of all sections within Directive 2001/83/EC, as amended, that are explicitly relevant to radiopharmaceuticals, can be seen in Table 6. Nevertheless, it must be kept in mind that this Directive must have been transposed to the national law, hence there might be some discrepancies in the interpretation of the Directive, both in general and regarding radiopharmaceuticals, between the member states.

Article	Chapter	Content
Article 1	**Definitions**	Definitions of Radiopharmaceutical, Radionuclide generator, Kit, Radionuclide precursor
Article 3	**Scope**	This directive does not pertain to magistral & official formulas; radionuclides in the form of sealed sources
Article 4	**Scope**	Obligation to radiation protection
Article 6	**Marketing authorization**	Marketing authorization required for radionuclide generators, radionuclide kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals
Article 7	**Marketing authorization**	Marketing authorization not required for radiopharmaceuticals prepared at the time of use by an individual or an authorized establishment, as per national regulations. This authorization is applicable exclusively within approved healthcare facilities, using authorized radionuclide generators, kits, or radionuclide precursors in adherence to the manufacturer's instructions (“extemporaneous preparation”)
Article 11	**Marketing authorization**	Additional requirements for Summary of Product Characteristics (SmPC) for radiopharmaceuticals – full details of internal radiation dosimetry; additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, the specified maximum storage time within which any interim preparation, such as an eluate or the ready-to-use pharmaceutical, will adhere to its specifications
Article 63	**Labelling and Package leaflet**	Exemption of certain particulars on the labelling of outer packaging and immediate packaging and package leaflet if the product is not intended for self-administration
Article 66	**Labelling and Package leaflet**	Specific requirements for labelling of outer packaging and immediate packaging of radiopharmaceuticals
Article 67	**Labelling and Package leaflet**	Need for a detailed instruction leaflet for radiopharmaceuticals, radionuclide generators, radionuclide kits or radionuclide precursors

Article 83	**Wholesale distribution of medicinal products**	The provisions of this Directive shall not prevent Member States from imposing stricter requirements concerning the wholesale distribution of radiopharmaceuticals
Annex I		Additional requirements for radiopharmaceuticals in relation to the dossier regarding chem-, bio-, pharm-, tox- and pharmacology tests of the medicinal product; and clinical documentation

Table 6: Articles of the Directive 2001/83/EC dedicated to radiopharmaceuticals.(38)

Commission Directive (EU) 2017/1572 in the radiopharmaceutical context

Commission Directive (EU) 2017/1572, respectively Directive 2003/94/EC do not provide any specific provisions or regulations for radiopharmaceuticals and the directives do not even mention the term "radiopharmaceutical" within the text. Moreover, the directives lack explicit considerations and distinctions among diagnostic, therapeutic, and theranostic medicinal products (encompassing radiopharmaceuticals), hence necessitating strict adherence to requirements outlined in the directives for all medicines. Therefore, although radiopharmaceuticals possess unique and distinct characteristics, the same GMP requirements must be followed as for conventional medicines, when not prepared as magistral/official formulas or as extemporaneous preparation, as these are generally exempted from the provisions of the directives.

Directive 2001/20/EC versus Regulation 536/2014 in the radiopharmaceutical context

As previously highlighted, Directive 2001/20/EC and Regulation 536/2014 exhibit distinct approaches in the regulation of clinical trials across the EU, including the specific realm of radiopharmaceuticals. Directive 2001/20/EC did not specifically address radiopharmaceuticals, lacked exceptions or provisions explicitly dedicated to radiopharmaceuticals and, furthermore, the term “radiopharmaceutical” was not even stated within the text of the Directive. Consequently, a manufacturing license and hence the compliance with GMP was required for all radiopharmaceuticals investigated in the clinical trials, encompassing even the extemporaneous preparations. However, despite these stringent requirements, certain exceptions existed. When intended for in-house use, magistral and official preparations, have been exempted from the need for a manufacturing license and thereby the compliance with GMP due to their specific nature and purpose of small-scale as well as case-by-case production, hence relevant to most radiopharmaceuticals. Nevertheless, regardless of the potential applicability of this exemption to radiopharmaceuticals, Directive 2001/20/EC imposed a substantial regulatory burden on the conduct of clinical trials investigating radiopharmaceuticals.

Upon the adoption of the Regulation 536/2014 several things were set in motion, extending to radiopharmaceuticals, which received particular attention through several provisions within the Regulation, specifically through the Articles 2, 61, 63, 68 and 91. The definition of 'radiopharmaceutical' under this Regulation is outlined in Article 2 of General provisions, which, however, refers to Article 1 of Directive 2001/83/EC for the applicable definition (see chapter Directive 2001/83/EC in the radiopharmaceutical context):

1. For the purposes of this Regulation, the definitions of […] ‘radiopharmaceutical’ […] set out in points […] (6) […], of Article 1 of Directive 2001/83/EC apply.(47)

Despite the Regulation being adopted 21 years after Directive 2001/83/EC, the applicable definitions have remained unaltered. Nevertheless, the most significant changes in regard to radiopharmaceuticals are defined in Chapter IX, focusing on the Manufacturing and Import of IMPs and AMPs, specifically

in the Articles 61 and 63. These articles state that radiopharmaceuticals used as diagnostic IMPs, along with magistral and official preparations, are exempted from marketing and import authorization requirements as well as compliance with GMP requirements, in case they are prepared in hospitals, health centres, clinics, by pharmacists or other legally authorised persons and are intended to be used within authorised facilities taking part in the same clinical trial within the same Member State:

Article 61

1. The manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an authorisation.

[…]

5. Paragraph 1 shall not apply to any of the following processes:

[…]

(b) preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;

(c) the preparation of medicinal products referred to in points (1) and (2) of Article 3 of Directive 2001/83/EC [magistral & official formulas] for use as investigational medicinal products, where this process is carried out in hospitals, health centres or clinics legally authorised in the Member State concerned to carry out such process and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State.

Article 63

1. Investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ('good manufacturing practice').[…]

2. Paragraph 1 shall not apply to the processes referred to in Article 61(5).(47)

This could lead to a potential exemption from marketing authorization as well as GMP compliance also for therapeutic as well as theranostic radiopharmaceuticals, when registered as magistral or official preparations as an IMP, hence prepared according to a prescription in hospital pharmacies for individual patients. However, these exemptions are not applicable to AMPs used during the clinical trials, which must always adhere to GMP requirements regardless of their marketing authorization status. Exceptions from the requirements of labelling of outer packaging and immediate packaging are outlined in Article 68 of the Regulation, meaning that all diagnostic radiopharmaceuticals whether used as IMPs or AMPs do not need to adhere to the detailed outer packaging and immediate packaging labelling standards which are set out in Articles 66 and 67 of the Regulation, applicable for all other medicinal products including

extemporaneous preparations, magistral, official preparations as well as therapeutic and theranostic radiopharmaceuticals:

Article 66

1. The following information shall appear on the outer packaging and on the immediate packaging of unauthorised investigational medicinal products and unauthorised auxiliary medicinal products: (a) information to identify contact persons or persons involved in the clinical trial; (b) information to identify the clinical trial; (c) information to identify the medicinal product; (d) information related to the use of the medicinal product.

[…]

A list of information which is to appear on the outer packaging and immediate packaging is set out in Annex VI. (see APPENDIX)

Article 67

1. Authorised investigational medicinal products and authorised auxiliary medicinal products shall be labelled: (a) in accordance with Article 66(1) […]

Article 68

Articles 66 and 67 shall not apply to radiopharmaceuticals used as diagnostic investigational medicinal products or as diagnostic auxiliary medicinal products.(47)

Nonetheless, appropriate labelling of outer packaging and immediate packaging is required in order to ensure patient safety and the reliability and robustness of the data generated in the respective clinical trials. Last provision dedicated to radiopharmaceuticals within the Regulation refers to Article 91:

This Regulation shall be without prejudice to Council Directive 97/43/Euratom, Council Directive 96/29/Euratom […](47)

As these Council Directives establish guidelines for safeguarding the health of both healthcare professionals and the general public from the risks of ionizing radiation, including those related to medical exposure, this Article mandates appropriate radiation protection for everyone involved, including both clinical researchers as well as patients.

A thorough summary of all sections within Regulation 536/2014 that directly pertain to radiopharmaceuticals is presented in Table 7.

Article	Chapter	Content
Art. 2	**General provisions**	In the context of this Regulation, the definition of 'radiopharmaceutical' as outlined in Article 1 of Directive 2001/83/EC is applicable
Art. 61	**Manufacturing and Import of IMPs and AMPs**	No need for manufacturing and import authorization for radiopharmaceuticals used as diagnostic IMPs if their preparation is conducted within hospitals, health centres, or clinics by pharmacists or individuals duly authorized by the relevant Member State to perform such procedures, and if the IMPs are exclusively intended for use in hospitals, health centres, or clinics participating in the same clinical trial within that Member State No need for manufacturing and import authorization for medicinal products referred to in points (1) and (2) of Article 3 of Directive 2001/83/EC = magistral & official preparations for use as IMPs if their preparation is conducted within hospitals, health centres, or clinics by pharmacists or individuals duly authorized by the relevant Member State to perform such procedures, and if the IMPs are exclusively intended for use in hospitals, health centres, or clinics participating in the same clinical trial within that Member State
Art. 63	**Manufacturing and Import of IMPs and AMPs**	No need for the GMP compliance for he medicinal products described in Article 61
Art. 68	**Labelling**	Radiopharmaceuticals used as diagnostic IMPs or AMPs do not need to comply with the outer and immediate packaging labelling requirements in Articles 66 & 67 of this Regulation. Nevertheless, their outer and immediate packaging must be appropriately labelled to safeguard the subject's safety and ensure the reliability and robustness of the data generated during the clinical trial
Art. 91	**Miscellaneous Provisions**	The protection against the radiation should be properly ensured, hence this Regulation should be without prejudice to Council Directive 97/43/Euratom* and Council Directive 96/29/Euratom* (*Note: These Council Directives determine guidelines for the health protection of both healthcare professionals and the general public from the hazards of ionizing radiation; incl. in relation to medical exposure)

Table 7: Articles of the Regulation 536/2014 dedicated to radiopharmaceuticals.(47)

In general, the implementation of the Regulation 536/2014 marks a positive stride in overseeing clinical trials involving radiopharmaceuticals in the EU, by acknowledging their unique character and thus introducing exemptions from the need for marketing authorisation, compliance with GMP as well as the allowance of simplified labelling of outer packaging and immediate packaging – a notable departure from the provisions of Directive 2001/20/EC. Nevertheless, this applies only to diagnostic radiopharmaceuticals used as IMPs within the trials as the oversight falls short in addressing therapeutic and/or theranostic radiopharmaceuticals, presenting a gap that requires urgent attention. Given the rapid expansion of this field, a thorough revision is crucial to ensure comprehensive coverage and effective regulation of radiopharmaceutical clinical trials.

DISCUSSION AND CONCLUSION

The investigation into the impact of Regulation 536/2014 on radiopharmaceuticals, alongside with Directives 2001/83/EC, 2003/94/EC, 2001/20/EC, and Commission Directive (EU) 2017/1572, has yielded comprehensive insights into the regulatory landscape governing this distinct sector. It became evident that most of these legal frameworks fall short in acknowledging the intricacies of radiopharmaceuticals, as these decrees were established years ago, thus fail to adapt to the dynamic nature of nuclear medicine and so poses significant challenges to the industry. Notably, Directive 2001/83/EC, enacted over two decades ago, emerges as a candidate for urgent revision as the radiopharmaceutical requirements, procedures and definitions remained the same since its adoption, whereby the field of nuclear medicine expanded and developed tremendously in recent years. Commission Directive (EU) 2017/1572 that repealed the Directive 2003/94/EU, underscores the importance of GMP, and while this emphasis may be crucial for maintaining quality standards, the significant differences between radiopharmaceuticals and conventional medicines necessitate bespoke provisions in order to mitigate the substantial challenges posed by these disparities and to ensure that radiopharmaceutical research remains viable and accessible in Europe. Similar challenges were encountered in the realm of clinical research within the radiopharmaceutical field under Directive 2001/20/EC as the substantial burden imposed by this Directive, which was primarily designed for conventional medicines, hence contained no provisions devoted specifically to radiopharmaceuticals, hampered the progression of clinical research in the unique context of radiopharmaceuticals.

Nevertheless, the Regulation 536/2014 marked a significant stride in the right direction, being the pioneering legal document to explicitly acknowledge and embrace the unique character of radiopharmaceuticals. However, the path to comprehensive regulatory integration is far from complete as the current exceptions within the Regulation extend only to diagnostic radiopharmaceuticals used as IMPs in clinical trials, thus leaving all therapeutic and theranostic radiopharmaceuticals as well as diagnostic radiopharmaceuticals used as AMPs subject to entirety of the requirements outlined in the Regulation. These requirements include meticulous adherence to criteria such as need for marketing authorization, compliance with GMP, while adhering to all outer and immediate packaging labelling requirements. Exemptions do exist, but solely for instances when these radiopharmaceuticals are employed as magistral or official preparations. In addition, in the context of theranostic radiopharmaceuticals, compliance with GMP, marketing authorization as well as outer and immediate packaging labelling requirements becomes imperative. This requirements stem from the nuanced nature of theranostic applications, meaning that if a therapeutic agent is used as an IMP, alongside with a diagnostic agent fulfilling the role of an AMP in order to study the effects of the therapeutic agent, then the diagnostic agent must either possess prior authorization or align with GMP standards, whereby the compliance with the outer and immediate packaging labelling standards remains questionable in this case, hence should be urgently addressed in the future. This presents a significant challenge in bringing

not only theranostic but also therapeutic radiopharmaceuticals to the market, imposing a considerable burden on the process. Despite these challenges, Regulation 536/2014 represents a promising commencement, nevertheless a sustained commitment to refinement is essential in order to create a regulatory environment that seamlessly accommodates the multifaceted dimensions of radiopharmaceuticals.

The validity of these findings is reinforced by the endorsement of top experts in the field, as documented in Oyen et al., 2023 and Patt et al., 2023(49,50). According to these articles, urgent revisions to pharmaceutical legislation are essential in order to align with contemporary standards and to reflect current situation in nuclear medicine and radiopharmaceutical practices, starting with a comprehensive update of radiopharmaceutical definitions defined in the Directive 2001/83/EC. These updated definitions, covering substances, radiopharmaceuticals, kits, generators, and more, should form the cornerstone of a modernized regulatory framework, accommodating the unique aspects of radiopharmaceuticals and radiopharmacy practices. Furthermore, specific considerations for both industrial and in-house production (magistral and official preparations) of radiopharmaceuticals are crucial to drive innovation and harmonization within the EU, ensuring broader access and alignment with existing regulations. Additionally, it is imperative to establish centralized and EU-wide procedures, standardize marketing authorization and GMP conditions as well as to provide essential clarification regarding the protection against the ionising radiation, hence update the Regulation 536/2014. In general, as highlighted in these articles, leading experts, including the EANM and Nuclear Medicine Europe (NMEU), advocate for immediate action. Their collective voice urges the establishment of a dedicated and harmonized European policy, whereby recognizing radiopharmaceuticals as a distinct class of medicinal products with a tailored regulatory framework – an outcome aligned with the findings of this investigation.

In conclusion and considering these observations, Regulation 536/2014 did introduce positive changes, however, it is evident that these measures fell short to meet the comprehensive needs of the swiftly evolving radiopharmaceutical industry. Therefore, advocating for the incorporation of special provisions within regulatory frameworks emerges as a paramount need, whereby this appeal is further reinforced by the endorsement of the experts within the field who recognize the necessity for nuanced solutions. In general, these provisions should be crafted with a complex understanding of the unique attributes of radiopharmaceutical products, aiming not only to alleviate burdens but also to foster an environment where research can thrive. By doing so, the continued vitality and availability of radiopharmaceuticals within the European regulatory landscape can be ensured.

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APPENDIX

Annex VI of Regulation 536/2014.(47)

ANNEX VI

LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS

A. UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

A.1. **General rules**

1. The following particulars shall appear on the immediate and the outer packaging:

   (a) name, address and telephone number of the main contact for information on the product, clinical trial and emergency unblinding; this may be the sponsor, contract research organisation or investigator (for the purpose of this Annex this is referred to as the 'main contact');

   (b) the name of the substance and its strength or potency, and in the case of blind clinical trials the name of the substance is to appear with the name of the comparator or placebo on the packaging of both the unauthorised investigational medicinal product and the comparator or placebo;

   (c) pharmaceutical form, route of administration, quantity of dosage units;

   (d) the batch or code number identifying the contents and packaging operation;

   (e) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

   (f) the subject identification number and/or the treatment number and, where relevant, the visit number;

   (g) the name of the investigator (if not included in (a) or (e));

   (h) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

   (i) 'For clinical trial use only' or similar wording;

   (j) the storage conditions;

   (k) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity; and

   (l) 'Keep out of reach of children', except when the product is for use in trials where the product is not taken home by subjects.

2. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings or handling instructions may be displayed.

3. The address and telephone number of the main contact shall not be required to appear on the label if subjects have been given a leaflet or card which provides these details and have been instructed to keep this in their possession at all times.

A.2. **Limited labelling of immediate packaging**

A.2.1. *Immediate and outer packaging provided together*

4. When the product is provided to the subject or the person administering the medicinal product in an immediate packaging and outer packaging intended to remain together, and the outer packaging carries the particulars listed in section A.1., the following particulars shall appear on the immediate packaging (or any sealed dosing device that contains the immediate package):

   (a) name of the main contact;

   (b) pharmaceutical form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and, in the case of clinical trials which do not involve the blinding of the label, the name/identifier and strength/potency;

   (c) batch and/or code number identifying the contents and packaging operation;

(d) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number and/or the treatment number and, where relevant, the visit number; and

(f) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity.

A.2.2. *Small immediate packaging*

5. If the immediate packaging takes the form of blister packs or small units such as ampoules on which the particulars required in section A.1. cannot be displayed, the outer packaging provided shall bear a label with those particulars. The immediate packaging shall contain the following:

(a) name of the main contact;

(b) route of administration (may be excluded for oral solid dose forms) and, in the case of clinical trials which do not involve the blinding of the label, the name/identifier and strength/potency;

(c) batch or code number identifying the contents and packaging operation;

(d) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number/treatment number and, where relevant, the visit number; and

(f) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity.

B. UNAUTHORISED AUXILIARY MEDICINAL PRODUCTS

6. The following particulars shall appear on the immediate and the outer packaging:

(a) name of the main contact;

(b) name of the medicinal product, followed by its strength and pharmaceutical form;

(c) statement of the active substances expressed qualitatively and quantitatively per dosage unit;

(d) batch or code number identifying the contents and packaging operation;

(e) clinical trial reference code allowing identification of the clinical trial site, investigator and subject;

(f) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

(g) 'For clinical trial use only' or similar wording;

(h) the storage conditions; and

(i) period of use (expiry date or retest date as applicable).

C. ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

7. In accordance with Article 67(2), the following particulars shall appear on the immediate and the outer packaging:

(a) name of the main contact;

(b) clinical trial reference code allowing identification of the clinical trial site, investigator, sponsor and subject;

(c) 'For clinical trial use only' or similar wording.

D. REPLACING OF INFORMATION

8. The particulars listed in sections A, B and C, other than those particulars listed in paragraph 9, may be omitted from the label of a product and made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system, provided that the safety of the subject and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

9. The particulars referred to in the following points shall not be omitted from the label of a product:

(a) paragraph 1, points (b), (c), (d), (f), (j) and (k);

(b) paragraph 4, points (b), (c), (e), and (f);

(c) paragraph 5, points (b), (c), (e), and (f);

(d) paragraph 6, points (b), (d), (e), (h), and (i).