JPHSR Journal of Pharmaceutical Health Services Research
ROYAL PHARMACEUTICAL SOCIETY

Radiopharmaceutical preparations: what are the legislative differences across Europe?

Journal:	*Journal of Pharmaceutical Health Services Research*
Manuscript ID	Draft
Manuscript type:	Research Paper
Keywords:	Regulatory, Health Policy, International

Abstract: Objectives. Radiopharmaceuticals, since the discovering of the first medical application of radioactive isotope, have been essential therapeutics for the diagnosis and treatment of numerous diseases. Since the Directive 2001/83/EC entered in force, European regulatory authorities have established a harmonized framework to set quality requirements for the industrial production of radiopharmaceuticals. However, little is known about the harmonization of extemporaneous preparation of radiopharmaceutical preparations (EPRPs) among European countries. In this context, this paper aims to provide an overview of the national regulatory framework on the production of EPRPs of five European countries (i.e., UK, Spain, France, Germany, and Italy). Methods. Five different national regulatory frameworks were compared based on the results of a literature search on electronic databases (i.e. PubMed, Google scholar). Key findings. Unlike industrially-produced radiopharmaceuticals, the results highlighted that the regulatory framework on EPRPs is still not fully harmonized at the European level and many provisions are still regulated at local national laws. Similarities and differences exist among the European countries both regarding quality standards and educational courses the operators involved in the preparation of EPRPs have to attend. Conclusions. The regulatory framework on the EPRPs is still not harmonized at the European level, affecting the access to therapies of European citizens who are not equally guaranteed when an extemporaneous radiopharmaceutical has to be prepared to meet their needs.

Abstract

Objectives. Radiopharmaceuticals, since the discovering of the first medical application of radioactive isotope, have been essential therapeutics for the diagnosis and treatment of numerous diseases. Since the Directive 2001/83/EC entered in force, European regulatory authorities have established a harmonized framework to set quality requirements for the industrial production of radiopharmaceuticals. However, little is known about the harmonization of extemporaneous preparation of radiopharmaceutical preparations (EPRPs) among European countries. In this context, this paper aims to provide an overview of the national regulatory framework on the production of EPRPs of five European countries (i.e., UK, Spain, France, Germany, and Italy). **Methods**. Five different national regulatory frameworks were compared based on the results of a literature search on electronic databases (i.e. PubMed, Google scholar). **Key findings**. Unlike industrially-produced radiopharmaceuticals, the results highlighted that the regulatory framework on EPRPs is still not fully harmonized at the European level and many provisions are still regulated at local national laws. Similarities and differences exist among the European countries both regarding quality standards and educational courses the operators involved in the preparation of EPRPs have to attend. **Conclusions**. The regulatory framework on the EPRPs is still not harmonized at the European level, affecting the access to therapies of European citizens who are not equally guaranteed when an extemporaneous radiopharmaceutical has to be prepared to meet their needs.

Keywords

Radiopharmaceuticals; Extemporaneous preparations; European regulatory framework; Industrially manufactured radiopharmaceuticals.

1 Introduction

The current regulatory framework on medicinal products has stated strict rules manufacturers have to follow to assess the quality, safety and efficacy profiles of the products placed on the market. For industrially manufactured medicinal products, specific procedures have been established to allow the competent regulatory authorities to assess the benefit/risk balance of products. If the regulatory framework on manufacturing and marketing of industrial medicinal products is harmonized among the EU, the preparation compounding is mainly ruled at the national level. However, when an industrial medicinal product is not available on the market, an extemporaneous preparation can be compounded by pharmacists to meet the specific needs of a patient.[1] This second scenario is relevant also for radiopharmaceuticals. They are medicinal products containing radioisotopes labelling molecules or individual radioisotopes that are intended to be used either for diagnostic or therapeutic aims.[2] The development of nuclear medicine over time has been intrinsically correlated to the advances in chemistry, medicine and the development of radionuclides and radiolabelled compounds.[2] Since marketing authorization (MA) of the iodine-131 by the FDA in 1951,[3] the use of radioactive substances in clinics has risen for several applications. However, one of the main limitations of radiopharmaceutical use has been the reduced half-life of the radioactive compounds, which is not generally suitable for the shelf-life time required by a conventional pharmaceutical supply chain. Therefore, in parallel to the development of new radiopharmaceutical products, technological progress has provided significant innovations in their manufacturing process, opening to the development of kits or generators for allowing the preparation of radiolabelled compounds directly in hospitals. It is the case of technetium-99m, a radionuclide obtained by molybdenum. Since its short half-life, its clinical use in clinics has risen only after the development of the technology able to produce generators for the hospital preparation or to ensure a highly efficient and daily transport to hospitals. Not all radiopharmaceuticals can be industrially produced and, therefore, they must be prepared extemporaneously in authorized structures. However, the current European regulatory framework leaves plenty of room for national countries to regulate the extemporaneous preparation of radiopharmaceuticals in hospital settings, generating differences among the European countries in terms of the settings allowed to prepare such medicines categories and in the scientific background of the personnel allowed to carry out such activities. In this review, we discuss the current European regulatory framework on radiopharmaceuticals, focusing on the existing differences among the European legislations regarding their extemporaneous preparation in hospital settings.

2 Methods

To compare the different national legislations about extemporaneous production of radiopharmaceuticals, peer-reviewed articles on the legislation of radiopharmaceuticals have been searched, included some specific papers on History and extemporaneous preparation of radiopharmaceuticals. In particular, searches on electronic databases (i.e. PubMed, Google scholar) were performed using terms as (Radiopharmaceuticals AND legislation) OR (Radiopharmaceutical AND Europe) OR (Extemporaneous AND Radiopharmaceuticals). In the initial screen of the identified articles, a single researcher reviewed the title and abstract of each paper to filter out irrelevant literature and duplicate. The exclusion criteria were: Paper on the clinical use of RF, Non-UE legislation about RF or non-update papers about current legislation. Moreover, Searches on National legislation source were conducted on verified national websites and the most updated documents were downloaded and translated, namely: Germany, http://bundesrecht.juris.de/amradv/index.html; Spain, http://noticias.juridicas.com; UK, www.legislation.gov.uk; France, www.legifrance.gouv.fr; Italy, http://www.parlamento.it/leggi/deleghe/07200dl.html. The initial research was conducted in November 2019, and the final refresh occurred in October 2020. In total, among 243 papers obtained from the initially identified, the literature search was refined to 13 papers and 11 decrees from national law.

3 Scientific background

The history of radioactivity (and consequently radiopharmaceuticals) started in 1896 when Henri Becquerel discovered naturally occurring radioactivity by observing a discharge vacuum tube, which emitted fluorescent light when cathode rays hit it.[4] Starting from this serendipity, new frontiers have been opened in the use of radioactive materials in medicine.[4] In parallel, the discovery of novel artificial radionuclides enhances the scientific research on radioactive substances that can be chemically bonded to a stable material to be used as a marker of the latter. Radiopharmaceuticals have been commonly used in clinical practice since 1951 when the iodine-131 was approved by the FDA.[4] Over time, other radiopharmaceuticals based on iodine have also been tested, without positive results due to the poor physicochemical stability. Subsequently, iodine-131 was overcome in clinical use by technetium-99m driven by the development of the technology for producing technetium-99m generators.[4] The discovery of technetium-99m (from the Greek τεχνητός, meaning synthetic or artificial), which resulted in a more versatile radioactive material than other ones, occurred in the late 1930s by Carlo Perrier and Emilio Segrè.[6] This radionuclide is obtained by fission or by neutron activation of stable molybdenum. Initially, complicated chemical methods were necessary for the separation of technetium-99m from molybdenum-99 because of its short physical half-life. For this reason, technetium-99m required to be delivered to hospitals every day. Later in 1960, the technological progress in

technetium generators permitted to obtain the daily production of technetium-99m in the nuclear medicine department, by an elution procedure.[4] This new method of producing technetium from a generator get to start the "new age" for nuclear medicine, allowing to undergo numerous types of diagnostic exams. Based on their application and the emitted radiations, radiopharmaceuticals can be used for diagnosis or for treatment. For example, radiopharmaceuticals emitting alpha (α) and beta (β) particles are more frequently used as therapeutics, whereas those emitting β+ particles and gamma rays are used as diagnostics. α particles are generally emitted from the decay of only the heavy radioactive nuclei, such as radium.[6] β radiation arises from β decay, of which there are two main variants: β- and β+ decay.[7] β+ decay or positron emission is becoming increasingly more important in oncology through positron emission tomography (PET) imaging.[8] On the contrary, the use of β- radiation has been increased over time taking advantage of the development of radioisotopes such as iodine-131. Lastly, gamma (γ) rays have the smallest wavelength and the highest energy.[7] Several isotopes emitting γ rays have been used for diagnostic purposes (Table 1).[9]

4 The regulatory framework

The European harmonisation process in the pharmaceutical field started in 1965 with the adoption of Directive 65/65/EEC.[10] This directive stated provisions for enhancing the access to the market to new drugs, including radiopharmaceuticals. Radiopharmaceuticals were exempted from various aspects of the pharmaceutical legislation for a reasonably long period in Europe and kept with other exclusive products, including vaccines, blood-derived products, and allergens.[11] The only rules available at that time were on radiation protection and compliance to pharmacopoeia monographs. The Directive 89/343/EC, for the first time, extended the existing rules of medicinal products to radiopharmaceuticals compounds used as diagnostic or therapeutic agents. This directive was translated into the legislation of the EU Member States. The immediate consequence was the need to apply for obtaining the MA of radiopharmaceutical products that have been on the market for more than twenty years. This upgrade of regulatory framework posed no minor problems to manufacturers of radiopharmaceuticals since they have been obliged to submit a full dossier, including detailed data on preclinical and clinical trials, to obtain the marketing authorisation.[12] For those reasons, a simplified procedure was accepted by regulators: a single file of pharmacological, toxicological, and clinical support using available data or published literature was judged as appropriate. Data strictly linked to the product quality, including chemistry and pharmaceutical development, manufacturing process, containers and labelling are mandatory. The leaflet and the summary of product characteristics (SmPC) must be also prepared based on a template as well as other medicinal products.

According to the directive 2001/83/EC,[13] currently in force in the EU, radiopharmaceuticals can be classified into four groups, namely:

- ***Radiopharmaceutical preparation***. *"A radiopharmaceutical preparation is a medicinal product in a ready-to-use form suitable for human use that contains a radionuclide. The radionuclide is integral to the medicinal application of the preparation, making it appropriate for one or more diagnostic or therapeutic applications."* [13]
- ***Radionuclide generator***. *"A system where a radionuclide, identified as nuclide "father" characterized by a prolonged half-life, decays into a "daughter" radionuclide, also radioactive, with a short half-life, and separated by elution. Later used to produce a radiopharmaceutical preparation.* [13]
- ***Radiopharmaceutical precursor***. *"A radionuclide produced for the radiolabelling process with a resultant radiopharmaceutical preparation."* [13]
- ***Kit for radiopharmaceutical preparation***. *"In general, a vial containing the non-radionuclide components of a radiopharmaceutical preparation, usually in the form of a sterilised, validated product to which the appropriate radionuclide is added or in which the appropriate radionuclide is diluted before medical use. In most cases, the kit is a multidose vial and production of the radiopharmaceutical preparation may require additional steps such as boiling, heating, filtration, and buffering."* [13]

5 Radiopharmaceutical preparations

The directive 2001/83/CE regulates multiple aspects relating to drugs and radiopharmaceuticals: market authorization, manufacture and import, distribution, advertising, and pharmacovigilance. It contains provisions (e.g., article 6 and 7) for MA for industrially manufactured radiopharmaceuticals and their exemptions in certain cases for extemporaneous preparations, respectively.[12] The radiopharmaceuticals can be grouped into two categories: industrially manufactured and extemporaneously prepared radiopharmaceuticals (Table 2). The latter ones are generally accepted only when an authorized industrial radiopharmaceutical is not available on the market.

5.1 Industrially manufactured radiopharmaceuticals

As reported in Table 2, industrially manufactured radiopharmaceuticals can be subclassified based on the need for MA to be placed on the market. In most cases, the radiopharmaceuticals must be authorized by a regulatory authority based on the dossier submitted by the applicant. However, in some exceptional and justified cases, a radiopharmaceutical can be industrially manufactured without a specific MA: e.g., based on a physician request for a specific pathology and patient, for exclusive use on a specific patient. As well as other types of medicinal products, radiopharmaceuticals used in clinical trials can be industrially manufactured without MA, applying the GMP guidance. In the EU, the legislation related to

radiopharmaceutical to clinical trials is ruled by Regulation (EU) 536/2014. The regulation established a harmonized electronic submission and assessment process for clinical trials conducted in multiple member states, introduces increased transparency on information on clinical trials and fixes the highest standards for all participants in EU clinical trials.[14] The regulation differentiates between products intended for therapeutic and diagnostic indications. Radiopharmaceuticals for therapeutic indication must fulfil the same provisions of other types of medicinal products, following complete GMP regulation (Directive 2017/1572). On the contrary, for diagnostics radiopharmaceuticals, the authorization for manufacturing and import of the investigational medicinal products is not needed, as well as the compliance to GMP for their manufacturing.[15]

5.2 Extemporaneously prepared radiopharmaceuticals

Many radiopharmaceutical preparations are prepared in small-scale on-site regularly, often as a single dose for one patient, based on specific clinical needs (extemporaneously prepared radiopharmaceutical preparations, EPRPs). Commonly, EPRPs included: Magistral formula (prepared in a pharmacy following a medical prescription) and Officinal formula (that follows pharmacopoeia monograph) and both are intended to be supplied directly to the patients.[14] In Europe, the regulations about EPRPs vary among the European countries as no directive is approved. In the following paragraph, five countries were analysed: France, Germany, Italy, Spain, and the UK (Table 3).

5.2.1 France

France translated the Directive 89/343/EEC into the national regulatory framework by Law 92-1279/1992, which amended the French code of public health (Code de la Santé Publique). The law established that the commercial Radiopharmaceuticals must be manufactured in Pharmaceutical Establishments (“établissement pharmaceutiques”), whereas the extemporaneous preparations can be prepared in pharmacies. Le Code de la santé publique is the most important document in French health legal frame. The Code differentiates between community pharmacies (“officines de pharmacie”) and pharmacies for internal use (“pharmacie à l’usage intérieur”, PUI).[16] The definitions of radiopharmaceuticals and other translated from directive 2001/83/EC are described in art. L5121-1,. The articles L5125-1 and L5126-2 managed the exemptions for pharmacies to prepare medicinal products without MA. An “Officine” can prepare and dispense magistral and officinal formula (art. L5125-1). This is not applicable to radiopharmaceuticals (articles L5121-1-7 and L5125-1-1) since their preparation is allowed only in a PUI. Commonly the PUIs are involved in the preparation of magistral preparations for a single patient. However, PUI should have to additional two authorisations (one to prepare radiopharmaceutical and one for the use and storage on radionuclide) for preparing radiopharmaceuticals.

5.2.2 Germany

"The Medicinal Products Act (Arzneimittelgesetz - AMG)" is the central legal framework for medicinal products in Germany. The Directive 2001/83/EC was translated in the § 7 AMG with the "*Ordinance on Radioactive Medicinal Products and Medicinal Products Treated with Ionizing Radiation" (Verordnung über Radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel, AMRadV)*.[17] However, some differences can be found in the German regulatory framework in comparison to the other European ones. For example, it does not include a specific definition for a Radiopharmaceutical kit. Moreover, according to AMRadV, no radioactive products can be placed on the German market without MA (§ 13 (2) AMG). Exception to such general rule are medicinal products that contain traces of natural radioactivity, radiopharmaceuticals for clinical trials or those prepared in pharmaceutically authorized institutions for not more than 20 treatments per week. Moreover, the MA is not needed for some radioactive products (prepared in a hospital pharmacy or hospital supplying pharmacy exclusively) by using generators, kits or radionuclide precursors and by following the instructions of the MA holder.

5.2.3 Italy

In Italy, industrially manufactured radiopharmaceuticals are ruled by the Legislative Decree 219/2006.[18] Extemporaneously prepared ones, as magistral and officinal preparations, are expressly excluded from its field of application. For such preparations, the quality standards are defined by "Norme di buona preparazione in medicina nucleare" (Good compounding practice in nuclear medicine, NBP-MN), published in the Official Pharmacopoeia of the Italian Republic.[19] The NBP-MN is the technical source of reference for all extemporaneous radiopharmaceuticals that are prepared in a clinical setting for diagnostic or therapeutic purpose. The radiolabelling autologous patient materials must be prepared following the same provisions. The NBP-MN defines the responsibilities, and the requirements to guarantee the quality and safety of radiopharmaceuticals. The general responsibility of the prescription is attributed to the nuclear physician, whereas the preparations must be managed in the nuclear-medicine department. All the operations that require the manipulation of radionuclides to prepare a radiopharmaceutical should be carried out in compliance with the national legislation on protection from ionizing radiation. Moreover, the NBP-MN included provisions for the calculation of specific activity of radiopharmaceuticals, control of radionuclide impurities, decontamination, and disposal of radioactive waste. The current regulatory framework does not formally prohibit physicians to prescribe industrially produced radiopharmaceuticals out of the indication contained in the Summary of Product Characteristics. An exception is given by the hospital preparation of the radiopharmaceuticals. According to the decree of the Minister of Health of 19 November 2003, nuclear medicine centres of public or private hospital structures with PET tomograph and cyclotron are authorized

to prepare extemporaneously 2-[18F]-fluoro-2-deoxy-D-glucose ([18F] FDG). This decree is still in force even if industrially manufactured radiopharmaceuticals are now authorized for the market.

5.2.4 Spain

The Spanish regulatory framework on radiopharmaceuticals is founded on the "Law on Medicines" (Ley del medicamento) 25/1990,[20] which was then abrogated by the Royal Decree 479/1993 and the Royal Decree 1345/2007. The Royal Decree 1345/2007 included the definitions of radiopharmaceuticals, precursor, kits, and generator and, in section 3 -article 46, states that all radiopharmaceuticals that are placed on the market should obtain a MA.[21] However, as well as other European countries, the Spanish legislation provides the same exemptions (art. 47) for extemporaneous preparation made with authorised kits/ generators/precursors, autologous cell preparations, or PET radiopharmaceuticals, always made in a radiopharmacy unit and under the supervision an expert. Moreover, according to the Spanish legislation, the extemporaneous preparation of radiopharmaceuticals is only permitted, for non-commercial purposes, to be used in clinical investigations or for diagnostic/therapeutic protocols for which the quality, safety and efficacy are considered acceptable. The radiopharmacy units (i.e., "radiofarmacias") are competent for the preparation of radiopharmaceuticals as magistral and officinal preparations, and those for PET. The commercial radiopharmacies should be authorised to prepare single or multi-dose vials and to distribute them to the neighbouring nuclear medicine departments, which are too small to have a hospital radiopharmacy.

5.2.5 United Kingdom

The UK was one of the first countries in Europe to concern radiopharmaceuticals as pharmaceutical products with the introduction of the "The Medicines Act 1968",[22] which is the major legal source in the UK regulatory framework on medicinal products, together with the "The medicines for human use Regulation.[23] According to UK legislation, radiopharmaceuticals are defined as "specials", which are products produced without a MA based on a prescription of authorized healthcare professional and under his responsibility, to meet a special need for a specific patient. Such products can be prepared both in GMP-certified industrial sites or in sites that received specific authorization by the competent authorities. Indeed, for productions of small-scale productions, including experimental drugs, the Medicines and Health products Regulatory Agency (MHRA) releases "special" manufacturer licenses, which can also be granted to authorized pharmacies (registered pharmacies), based on a GMP certification.[14] Among the staff requirements of this site, the release of a manufacturer "special" license is related to the compliance to the specific requirement for the personnel and the site, other than the identification of a pharmacist in charge of the production and quality control. Such

provisions are not required for radiopharmacy, but the pharmacist in charge must demonstrate experience and appropriate training.

6 Professionals authorized for the preparation of radiopharmaceuticals

A major challenge in the small-scale preparation of radiopharmaceuticals in the future is training and the expertise of persons in charge of their preparation. For the industrially manufactured radiopharmaceuticals, a qualified person is required after the directive EC 2001/83 entered in force as well as other medicinal products.[2] The qualified people must demonstrate a professional background (usually pharmacists, in some countries also chemists, biologists or related experts) with appropriate experience and training in quality assurance.[24] For the extemporaneously prepared radiopharmaceuticals, the regulatory framework is more fragmented around Europe. The Spain legislation allows both chemist and pharmacist to study "Radiopharmacy" as a multidisciplinary speciality course. The education requires 3 years of hospital residency and a final exam to be responsible for a radiopharmacy unit. In other European countries, no professional figure is exactly identifiable with a radiochemist or a radiopharmacist. The operators employed in the Nuclear Medicine Structures therefore may have different scientific backgrounds. To address, at least in part, this educational deficiency, the European Society of Nuclear Medicine (EANM) has set up a European Radiopharmacy Certification which can be obtained by people with a university degree in scientific subjects (like chemistry or pharmacy). The certificate is released to everyone who completes a specific programme of education and two years of practical experience in the field. The programme is organized by members of the Radiopharmacy Education Board and is valid for a duration of 5 years. [25]

7 Conclusion

The enactment of directive 2001/83/CE introduced a harmonized regulatory framework on industrially manufactured radiopharmaceuticals among the EU countries. However, considering the peculiarities of such medicines class, a part of them is still prepared extemporaneously in authorized facilities to satisfy the specific needs of patients. However, the regulatory framework on the extemporaneous radiopharmaceutical preparation and the specific expertise of the compounders is mostly demanded to single initiatives of European countries. In this situation, the European citizens' access to therapies is not equally guaranteed when an extemporaneous radiopharmaceutical has to be prepared to meet their needs.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Bibliography

1. Minghetti P., Pantano D., Gennari C.G.M., Casiraghi A., Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe, Health Policy (New York) 117 (2014) 328–333.
2. Sharma N., Kaur H., Sharma R.K., Radiopharmaceuticals Regulations: Current Scenario and the Way Forward, Applied Clinical Research, Clinical Trials and Regulatory Affairs 4 (2017) 183.
3. Staum M.M., Landmarks and Landmines in the Early history of Radiopharmaceuticals, J Nucl Med Technol 20 (1992) 209-213.
4. Carlsson S., A Glance at the History of Nuclear medicine. Acta Oncologica 34 (1995) 1095-1102.
5. Donya M., Radford M., ElGuindy A., Firmin D., Yacoub M.H., Radiation in medicine: Origins, risks and aspirations, Glob Cardiol Sci Pract 2014 (2014) 437-448.
6. Sharma S., Baldi A., Sing R.K., Sharma R.K., Regulatory framework of radiopharmaceuticals: current status and future recommendations, Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences (2018), doi: 10.26479/2018.0403.25.
7. Joyce M., Chapter 3 - Fundamentals of Radioactivity, In: Joyce, M. Nuclear Engineering – A conceptual introduction to nuclear power, Elsevier, 35-60.
8. Welsh J.S., Beta decay in science and medicine. Am J Clin Oncol., 30 (2007), 437-439.
9. World Health Organization, The international Pharmacopoeia, Available at: https://apps.who.int/phint/2019/index.html#p/home [web access: 30th September 2020]
10. European Council, Directive 65/65/CEE. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:31965L0065&from=IT [web access: 30th September 2020].
11. Sharma S., Jain S., Baldi A., Singh R., Sharma R., Intricacies in the approval of radiopharmaceuticals-regulatory perspectives and the way forward. Current sciences 116 (2019) 47.
12. Salvadori P.A., Radiopharmaceuticals, Drug development and pharmaceutical regulations in Europe, Current Radiopharmaceuticals 1 (2008) 7.
13. European Parliament and the Council, Directive 2001/83/EC, Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32001L0083&from=en [web access: 30th September 2020].
14. Decristoforo C. Penuelas I, Towards a Harmonised radiopharmaceutical regulatory framework in Europe? Q J Nucl Med Mol Imaging 53 (2005) 394-401.

15. Penuelas I., Vugts D., Decristoforo C., Elsinga P.H., The new regulation on clinical trials in relation to radiopharmaceuticals: when and how will be implemented? EJNMMI Radiopharmacy and chemistry 4 (2019) 1-5.

16. Code de la santé publique. Available at: www.legifrance.gouv.fr [web access: 30th September 2020].

17. Verordnung über radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel (AmRadV). Available at: http://bundesrecht.juris.de/amradv/index.html [web access: 30th September 2020]

18. Decreto legislativo 219/06. Available at: http://www.parlamento.it/leggi/deleghe/07200dl.htm [web access: 30th September 2020]

19. Farmaceopea Ufficiale della Repubblica Italiana, Edizione XI supplemento.

20. Ley del Medicamento 25/1990. Available at: http://noticias.juridicas.com [web access: 30th September 2020]

21. Royal decree 1345/2007. Available at: http://noticias.juridicas.com [web access: 30th September 2020]

22. The Medicines Act, Available at: www.legislation.gov.uk [web access: 30th September 2020].

23. The Medicines for Human Use Regulation, Available at: www.legislation.gov.uk [web access: 30th September 2020].

24. Decristoforo C, Challenges in the Small-scale preparation of radiopharmaceuticals- a European perspective. FABAD J. Pharm. Sci. 32 (2007) 131-138.

25. EANM Radiopharmacy course : https://www.eanm.org/esmit/radiopharmacy-course-2 [web access: 30th September 2020].

Table 1. Chemical-physical characteristics of some radionuclides used in PET e SPECT, for nuclear medical diagnostics and relative application [**Error! Bookmark not defined.**, **Error! Bookmark not defined.**].

Radionuclide	**T ½**	**β+ (KeV)**	**β- (KeV)**	**Energy γ (KeV)**	**Note**
Iodine-131	8.04 d		606	284,364,673	For diagnostic (SPECT) and therapeutic purpose
Iodine-123	12.8 h		low energy β- rays	27,159	For SPECT thyroid exams
Technetium-99m	6 h			140	Used for labelling numerous kit
Fluorine-18	110 m	640		511	Help in numerous oncology and neurology PET exam

Table 2. Regulatory sources for radiopharmaceuticals preparations

Industrially manufactured radiopharmaceuticals	**Extemporaneously prepared radiopharmaceuticals**
With marketing authorization • Directive 2001/83/CE **Without marketing authorization** • Directive 2001/83/CE, art 5 **Clinical trials** • Regulation (EU) 536/2014. • Directive 2017/1572 (GMP Regulation)	**Officinal formula** • Directive 2001/83/CE, art 3 • National legislation **Magistral formula** • Directive 2001/83/CE, art 3 • National legislation **Clinical trials** • Regulation (EU) 536/2014.

Table 3. Extemporaneous preparation of radiopharmaceuticals in different European countries.

Country	Extemporaneous preparation of radiopharmaceuticals	Personnel authorized to the preparation
France	Radiopharmaceuticals are prepared only in PUI	Pharmacist with appropriate training on radiopharmaceutical (i.e., Course of commissariat puor l'energie atomique CEA)
Germany	Radiopharmaceuticals can be prepared without a marketing authorisation or clinical trial status if they are prepared in a pharmaceutically authorised institution for not more than 20 applications per week.	Qualified persons for radiopharmaceuticals need a diploma in pharmacy, chemistry, biology, human or veterinary medicine and at least three years' experience in the field of nuclear medicine
Italy	Radiopharmaceuticals can be prepared in hospital pharmacies	The NBP-MN define the needed personnel
Spain	Radiopharmaceuticals are only prepared in radiopharmacies	Pharmacist with a specialization course in Radiopharmacy (3 years)
UK	Radiopharmaceuticals can be prepared only in structures with a "special license" and under the responsibility of a pharmacist	Pharmacist with (no mandatory) appropriate experience and training