Radiopharmaceuticals - are their peculiarities adequately reflected in European legislation?

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List of Abbreviations

Abbreviation	Explanation
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for healthcare products)
AFSSAPS	Agence française de sécurité sanitaire des produits de santé (French Agency for health product safety)
AMG	Gesetz über den Verkehr mit Arzneimitteln (The Medicinal Products Act)
ApBetrO	Verordnung über den Betrieb von Apotheken (Ordinance on Operating a Pharmacy)
API	Active Pharmaceutical Ingredient
APOG	Gesetz über das Apothekenwesen (The Law on Pharmacies)
ARSAC	Administration of Radioactive Substances Advisory Committee
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Medicinal Products and Medical Devices)
CEP	Certificate of Suitability of the Monographs of the European Pharmacopoeia
CHMP	Committee for Human Medicinal Products
CPMP	Committee for Proprietary Medicinal Products
CP	Centralised Procedure
CSP	Code de la Santé Publique (Code of Public Health)
DGN	Deutsche Gesellschaft für Nuklearmedizin
e.g.	exempli gratia (for example)
EANM	European Association for Nuclear Medicine
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCP-V	Verordnung über die Anwendung der guten klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (Ordinance on applying Good Clinical Practice when performing Clinical Trials with Medicinal Products for Human Use)
GMP	Good Manufacturing Practice
GRPP	Good Radiopharmacy Practice
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MRP	Mutual Recognition Procedure

MS	Member State (of the European Union)
NHS	National Health System
PET	Positron Emission Tomography
Ph.Eur.	European Pharmacopoeia
PIC/S	Pharmaceutical Inspection Convention / Scheme
PIL	Patient Information Leaflet
PUI	Pharmacie à l'Usage Intérieure (Pharmacy for Internal Use)
QA	Quality Assurance
QP	Qualified Person
RD	Real Decreto (Royal Decree)
RP	Radiopharmaceutical(s)
SERFA	Sociedad Española de Radiofarmacia (Spanish Society of Radiopharmacy)
SmPC	Summary of Product Characteristics
SNRPH	Syndicat National des Radiopharmaciens (National Union of Radiopharmacists)
SoFRa	Société Française de Radiopharmacie (French Society for Radiopharmacy)
SPECT	Single Photon Emission Computed Tomography
SYNPREFH	Syndicat National des Pharmaciens des Etablissements Publics de Santé (National Union of Pharmacists in Public Health Care Establishments)
UK	United Kingdom
USA	United States of America
WNA	World Nuclear Association
ZLG	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (Central Authority of the Federal States for Health Protection with regard to Medicinal Products and Medical Devices)

1. Introduction

"Radiopharmaceuticals" (RP) are a heterogeneous class of medicinal products characterized by the fact that they contain one or more radioactive isotopes. Those isotopes decay spontaneously under emission of ionising radiation that is used for various medical purposes. The use of RP covers a broad range of procedures such as diagnosis (single photon emission computed tomography, SPECT; and positron emission tomography, PET), radiation therapy (oncology and palliative pain management) as well as early research and clinical development employing radio-labeled molecules (e.g. pharmacokinetics, metabolism, receptor-binding studies). In contrast to classic medicinal products, RP contain very small amounts of active substances that usually do not trigger pharmacodynamic effects *(Schirbel, 2006)*. A non-exhaustive overview of radioactive substances and isotopes used for medical purposes can be found at *Schirbel, 2006,* or *Cortès-Blanco, 2003,* and some examples are included as Appendix A to this thesis.

The relevance of RP in the medical sector is illustrated by the following figures: According to the Danish Medicines Agency "radiopharmaceuticals are used in approximately 100,000 examinations a year in Denmark" *(www.legemiddelstyrelsen.dk, last visited on 11th February 2012)*. As Denmark has around 5,5 million inhabitants this corresponds to nearly 2 % of the population. Similar data are reported by the World Nuclear Association (WNA): "Over 10,000 hospitals worldwide use radioisotopes in medicine, and about 90% of the procedures are for diagnosis. […] In developed countries […] the frequency of diagnostic nuclear medicine procedures is 1,9 % per year. In the USA there are about 18 million nuclear medicine procedures per year among 305 million people, and in Europe about 10 million among 500 million people and the use of radiopharmaceuticals in diagnosis is growing at over 10% per year" *(WNA, 2011).* Noteworthy, "the most widely used radioisotope in diagnostic nuclear medicine is Technetium-99m. It is estimated that over 80 % of the nearly 25 million diagnostic nuclear medicine studies carried out annually are done with this single isotope" *(IAEA, 2007)*. In addition "PET-studies using ^{18}F-FDG, a ^{18}F-labelled analogue of glucose, account for 10% of all imaging procedures performed by using radiopharmaceuticals" *(IAEA, 2007),* and the use of this technique is constantly growing.

Radiopharmaceuticals are classified as "medicinal products" and consequently they are underlying the same regulations as non-radioactive medicinal products. In addition to the pharmaceutical legislation, laws concerning radiation protection of workers, general public and environment have to be followed by those aiming to manufacture, supply or use radioactive medicinal products. Although this thesis will not focus on radiation protection issues, the relevant laws on European level shall be mentioned here: The rules for radiation protection are laid down in Directive 96/29/EURATOM ("basic safety standards for the protection of the health of workers and the general public against the dangers arising from

ionizing radiation") and Directive 97/43/EURATOM ("health protection of individuals against the dangers of ionizing radiation in relation to medical exposure and repealing Directive 84/466/Euratom"). The rules of radiation protection (main goal: "safety of workers") are at certain points contradictory to the principles of Good Manufacturing Practice for medicinal products (GMP; main goal: "safety of product or safety of patient treated with product").

In order to categorise the heterogeneous group of RP, different criteria can be taken into consideration: They can be distinguished in medicinal products for diagnostic (SPECT, PET) and for therapeutic use based on the type and energy of radiation. Corresponding ATC codes are V09 and V10, respectively. Some radioisotopes actually are suited for both. Furthermore, RP can be grouped according to their physical half-lives: very short-lived (less than 20 min; e.g. C-11 or Rb-82) that need to be prepared almost next to the patients bedside, medium-lived that are suited for distribution over shorter distances (e.g. F-18, with a half-life of 107 min or Tc-99m allowing for a certain delivery radius around the production site) and longer-lived isotopes, that allow for commercialisation in Europe or the whole world out of one manufacturing site (examples: Y-90 with a half-life of 64,1 h or I-131 with 8,02 days). Generator-produced radioisotopes are another special class that do not really fit into the above categories: a long-lived mother-nuclide allows for distribution of the generator throughout the world while the short-lived daughter-nuclide requires preparation near to the site of administration and ensures minimal radiation exposure of the patient.

From a pharmaceutical point of view, most ready-to-use radioactive medicinal products are presented in the pharmaceutical form of "solution for injection" while few are available as oral dosage forms ("tablet", "capsule"); colloidal suspensions and radio-labeled patient's autologous cells complete the picture. Carrier molecules to be radiolabeled are available as lyophilized "kits" and radioactive precursors as "solution" or "generators". "Radionuclide generator" is a unique dosage form of RP: a device providing continuous access to a certain radioisotope in the form of solution or gas for inhalation. "Among radiopharmaceuticals, the ready-to-use forms account for 20-30 % of all products administered while 70-80 % are marketed in the form of radionuclide precursors, generators and kits that need to be assembled prior to administration to the patient in a healthcare establishment" *(de Beco, 2007).*

For the purposes of this thesis a categorisation according to the legal status of the RP seems to be most adequate. Noteworthy, there is a great number of RP administered without marketing authorisation (MA). Basically 4 groups can be distinguished

"1) ready to use licensed RP's: prepared and delivered to hospital by RP-manufacturer; 2) RP's prepared just before use in the nuclear medicine department using licensed labelling kits and [..] a licensed […] generator or licensed precursor radionuclide;

3) RP's synthesised on site […] starting from raw materials and in house cyclotron produced radionuclides and,

4) radiolabeled patients' autologous blood cells" *(Verbruggen, talk, 2007*).

These different ways of providing RP are a result not only of the peculiarities of RP such as the short half-life making a production near the site of application indispensable but also of the historic development: RP have not originated from the pharmaceutical industry. "Nuclear medicine was developed in the 1950s by physicians with an endocrine emphasis, initially using Iodine-131 to diagnose and then treat thyroid disease" *(WNA, 2011).* Scientists from Brookhaven National Laboratory, USA first described the synthesis of Fluorine-18-labeled fluorodeoxyglucose (^{18}F-FDG) in 1977, starting the "evolution of the PET as clinically useful imaging modality" *(IAEA, 2007)*. Classical pharmaceutical industry is still not the main source of RP. The group of players acting in this field is as heterogeneous as the class of medicinal products: it ranges from (university) hospitals, only preparing products needed for the hospital ("in-house"), over small public as well as private institutions supplying nuclear medicine departments in their neighbourhood, to globally acting industrial companies selling kits and isotopes almost worldwide.

As for all medicinal products, "Preparation and use are regulated by a number of EU directives, regulations and rules that have been adopted by member states. […] Specific articles have been put in place concerning radiopharmaceuticals that are to receive marketing authorization or are prepared starting from licensed products (radionuclide generators, labelling kits and precursor radionuclides). However, radiopharmaceuticals may also be prepared outside the marketing authorization track or used outside the indications they have been registered for." *(Elsinga, 2010).*

To understand today's regulatory environment, it is important to look back to the days when RP were initially subjected to the pharmaceutical legislation: In Europe, it was only in 1989 when Council Directive 89/343/EEC extended the scope of Directives 65/65/EEC ("common rules for medicinal products") and 75/319/EEC ("marketing authorisation procedures") on RP. Before, the "applicable rules were on radiation protection and compliance to Pharmacopoeial monographs. As of 1992, European Pharmacopoeia had more than 30 monographs covering the majority of routinely used radiopharmaceuticals." *(Salvadori, 2008).* With Directive 89/343/EEC, "additional provisions for radiopharmaceuticals" were laid down, as it was understood that the "provisions laid down by law, regulation or administrative action for proprietary medicinal products, although appropriate, are inadequate" for RP *(Directive 89/343/EEC)*. At that time definitions for RP were introduced that have not been changed until today. It was clarified that a MA was "required for generators, kits, precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals" *(Salvadori, 2008)*. Another remarkable point was the exemption for the "extemporaneous preparation" that was

introduced into the law, taking into account that the finished product is prepared near the patients' bedside: RP "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 authorised generators, kits or precursor radiopharmaceuticals in accordance with the manufacturer's instructions" do not require a MA. In addition the Directive set specific requirements for SmPC and labelling of RP, in particular the request for information about details of the extemporaneous preparation in the package leaflet, if applicable.

Directive 89/343/EEC was rather short, comprising of only 9 Articles, and although it had the goal to "take into account the special nature of RP", according to its introductory text, it had a large impact on the existing landscape of RP. When Directive 89/343/EEC came into force it was for implementation within 2 years. "The immediate consequence was the need to file a registration of radiopharmaceutical products, about 50, that have been on the market for more than twenty years. This posed no minor problems: on one side many industries involved did not have experience to manage the full registration dossier, on the other side running all expected protocols, including preclinical and clinical trials would require years. An abridged procedure was then accepted by regulators: a single file of pharmacological, toxicological and clinical support using available data or published literature was judged as appropriate." *(Salvadori, 2008)*. The CPMP issued a template for the SmPC to be used to develop individual package leaflets and only the quality part of the dossier had to be elaborated by each applicant. "Difficulties were immediately evident in applying standard regulations to radioactive compounds, many of them with remarkably short half-life. Similar difficulties were experienced by the various reviewers in adopting common assessment standards, in particular dealing with what was for several a completely new subject area. On top of this, the peculiar nature of this kind of a medicinal product – e.g. limited number of items per batch, the need of multiple batches per week – made it very difficult to align what was due to what was possible. Not to mention the endless discussions between applicant and regulators concerning what to define as *strength* in a short-lived diagnostic agent." *(Salvadori, 2008)*. To reduce the workload an "Abridged and Coordinated Registration Procedure for all radiopharmaceuticals that have been marketed before 1992 in any EU country or were compliant with a monograph of the European Pharmacopoeia has been installed. […] To facilitate and expedite the procedure of documentation evaluation, a working group was established with experts from all Member States between which the workload of evaluation was distributed. Each country evaluated one product type on the basis of common criteria previously established and referred its assessment report to other countries who accepted the assessment by the rapporteur country on the principle of mutual recognition." *(Cortès-Blanco, 2003).*

Recently, 20 years after Directive 89/343/EEC extended the pharmaceutical legislation on RP and the European States transformed the RP into properly authorised medicinal products by a worksharing procedure, it was still postulated that “[…] most of the existing rules are intended for medicinal products in general and are not specific for radiopharmaceuticals. Moreover, some of the current regulations do not take into account the special characteristics of radiopharmaceuticals, such as their short shelf life, which is due to the short physical half-life of the radionuclide, the small scale of the preparation and the low or absent toxicity of the final product […]” *(Elsinga, 2010).*

2. Goals of the Thesis

This Master Thesis will investigate how the peculiarities of radiopharmaceuticals are currently reflected in EU legislation. Different ways of transformation into national law of selected Member States shall be compared. A potential need for improvements especially when considering future potential clinical or technical developments shall be evaluated. The basis for the discussions will be a survey of applicable laws and ordinances as well as guidance documents published by regulatory bodies on the subject of RP on EU level and in Germany, United Kingdom, France and Spain.
In particular, the thesis will try to contribute to answer the following questions:

1) Which healthcare establishments are authorised for extemporaneous preparation of RP in the different Member States? What is their legal basis?

2) Which quality standards are applicable to the manufacture of different types of radiopharmaceuticals? What are the main differences to conventional “full GMP” according to Directive 2003/94/EC and the EU-GMP-guideline?

3) Which personnel is involved in manufacturing and release of RP, what kind of education and qualification is required according to the law of the respective Member State?

4) How is the situation regarding innovation and clinical development of new radiopharmaceuticals? Can hindrances by certain legal regulations be identified?

5) Are there concepts / achievements in other Member States that should be adopted to improve the German system? What prerequisites or legal changes would be necessary?

3. Legislation and guidances: EU and selected Member States

3.1 European Union (EU)

3.1.1 Directive 2001/83/EC

The community code for medicinal products in the European Union gives the legal frame for all Member States. It has to be transformed into the national law. Directive 2001/83/EC, as amended, contains definitions for radiopharmaceuticals, kits, precursors and generators in Article 1, 6. – 9.. This definitions is unchanged since it has been issued on 6th November 2001 and is originating from Directive 89/343/EEC.

All parts of Directive 2001/83/EC, as amended, that are explicitly related to RP are summarised in Table 1. Apart from the definitions only a few other sources of information are dedicated solely to RP: In Art. 3 the scope of the directive is explained, with exemptions for "magistral" and "officinal" formulas prepared in a pharmacy as well as for radionuclides in the form of sealed sources.[1] Most important for this thesis are Article 6 and Article 7. They represent the implementation of Article 2 of Directive 89/343/EEC into the community code. Article 6 clearly states that a MA is required for "industrially manufactured RP" and "for precursors, kits and generators". However, according to Article 7 the combined product prior to administration is exempted from the need for MA as long as the preparation is done by "a person or an establishment authorised, according to national law" leaving it to the Member States to empower specific entities for extemporaneous preparation of RP:

The provisions of Articles 11, 66 and 67 are related to SmPC, Labelling and PIL, respectively, and name certain requirements to be added for RP in addition to the requirements for conventional medicinal products. According to Article 63 (3) the Member States may waive some of the requirements for PIL and Labelling if medicinal products are not handed over directly to patients. This applies to the majority of RP. Article 83 opens the possibility for the Member States to regulate the distribution of RP deviating from the distribution of conventional medicinal products.

In Part III of the Annex I the requirements for the dossier for Marketing Authorization Application are listed and requirements for additional information for RP are made.

[1] A "sealed source" is a radioactive element or substance that is encapsulated in a tight shell of non-radioactive material.

Table 1: Articles of Dir 2001/83/EC related to radiopharmaceuticals

Source	Text	Meaning
Art. 1	*For the purpose 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. 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.*	Definitions
Art. 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 radionuclide in the form of sealed sources.*[2]	Scope
Art. 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.* *[…]*	Relation to rules on radiation protection
Art. 6	*Marketing authorisation* *[…]* *2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.*	Need for MA for RP

[2] The official German translation says exactly the opposite: http://ec.europa.eu/health/files/eudralex/vol-1/index_en.htm (last visited on 20th January 2012)

Art. 7	*A marketing authorisation 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, kits or radionuclide precursors in accordance with the manufacturer's instructions.*	"Extemporaneous preparation"
Art. 11	*The summary of product characteristics shall contain, in the order indicated below, the following information:* *[…]* *11. for radiopharmaceuticals, full details of internal radiation dosimetry* *12. 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 specification.*	SmPC: special requirements
Art. 63	*[…]* *(3) When the product is not intended to be delivered directly to the patient, the competent authorities may grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet and that the leaflet must be in the official languages of the Member State in which the product is placed on the market*	Exemption from Braille
Art. 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 and address of the manufacturer,* *- the amount of radioactivity as specified in paragraph 2.*	Labelling: special requirements
Art. 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 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.*	PIL: special requirements
Art. 83	*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*	Distribution of RP
Annex I	*Part III* *Particular Medicinal Products* *2. Radiopharmaceuticals and precursors […]*	Requirements for MAA Dossier

A very recent example where the peculiarities of radiopharmaceuticals have been taken into consideration is Directive 2011/62/EU, amending Directive 2001/83/EC: RP are explicitly exempted from taking measures against counterfeit medicine:

Article 54

[…]
(o) for medicinal products other than radiopharmaceuticals referred to in Article 54a(1), safety features enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:
- verify the authenticity of the medicinal product, and
- identify individual packs,
as well as a device allowing verification of whether the outer packaging has been tampered with.

The following aspects may have lead to this exemption: a number of licenses are necessary for all entities involved in the manufacture and supply of RP (marketing authorisation, manufacturing license, wholesale distribution license on the one hand and on the other side handling license for radioactive substances). Therefore, the supply chain is well-controlled and secure. "Placebo"-drugs or other falsified products could easily be detected as the receiving hospital or physician usually performs a quality control before administration.

3.1.2 Directive 2001/20/EC

Directive 2001/20/EC, as amended, contains no exemptions or special provisions for RP. The term "radiopharmaceutical" is not mentioned in the text of this Directive. An option similar to the Article 7 of Dir 2001/83/EC is not foreseen on community level for novel RP under investigation. As a consequence, a manufacturing license would be required for all RPs in a clinical trial, both kit-based preparations and ready-to-use RP. Whenever a manufacturing license is needed the respective institution is automatically subjected to Directive 2003/94/EC as well as regular inspections by the competent authorities. However, for in-house use the institution may prepare exactly the same product, e.g. as an officinal preparation, without manufacturing license and adherence to the EU-GMP-guideline. Directive 2001/20/EC imposed a high burden especially on academic institutions and "made it extremely difficult for the academia or non-profit organizations to carry out their own clinical trials" *(Decristoforo, 2009).*

It shall be mentioned that the situation of RP in clinical trials is even more complex: not every (PET-)radiopharmaceutical used in a clinical trial is regarded as IMP and not every European authority requests a GMP-compliant manufacture of it. However, due to the limited time for this thesis this subject shall not be further elaborated. For information reference is made to Eudralex Volume 10 *(http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm)* and the website of the MHRA with a section about PET trials *(www.mhra.gov.uk, last visited on 11th February 2012)*.

3.2 Germany (DE)

3.2.1 General description

In 2006 the landscape in Germany was described by the following key points: "The preparation of radiopharmaceuticals started in large research centres. Today about 100 radiochemists work in about 20 PET centres and larger university hospitals, (almost) no pharmacists are involved in the field. Besides the hospitals, Germany has a large number of private nuclear medicine-institutes and practices. The daily preparation of "conventional" radiopharmaceuticals (e.g. ^{99m}Tc-RP) is done by technicians under the supervision of medical doctors." *(Decristoforo, talk, 2006).*

This description of the general situation in Germany still seems to be adequate in most points although recent changes in pharmaceutical law have strongly influenced the field. The German landscape of institutions producing and/or selling RP is characterised by hospital-based institutions, mostly with academic background, that predominantly produce for the in-house application, but also distribute their overcapacities to third parties based on MA. It is important to note that the compliance with the Medicinal Products Act in Germany is controlled by the Federal States, coming along with the acceptance of varying practices by different state authorities. In addition to licenses required by the pharmaceutical law every institution dealing with radioactive substances needs a handling license (Umgangsgenehmigung) according to the Ordinance on Radiation Protection (Strahlenschutzverordnung).

3.2.2 The Medicinal Products Act (Arzneimittelgesetz - AMG)

The Medicinal Products Act explicitly mentions RP at several sections. An overview is provided in Table 2. The definitions of RP are provided in § 4, sub-section 8: The German law did not adopt the definition from the European level exaclty as there is no definition for "kit". A "cold kit" may be subjected under § 4 (1): the definition of finished medicinal products ("Fertigarzneimittel"). Furthermore, radionuclide precursors and generators fulfil also the German definition of "radiopharmaceutical". The definitions of the terms "marketing" § 4 (17) and "reconstitution" § 4 (31) are also important to understand some recent developments with regard to RP.

Most important for all RP-related business is the prohibition of placing on the market as laid down in § 7 ("Verkehrsverbot"):

It shall be forbidden for radiopharmaceuticals […] to be placed on the market unless the authorisation to do so has been given by ordinance […].

The German legislators choose a very strict means as this prohibition of § 7 excludes the RP from the exemptions for magistral and officinal preparations in pharmacies (§ 13 (2) AMG; §§ 7 and 8 ApBetrO) and restricts the placing on the market to those cases explicitly outlined

in the corresponding Ordinance on RP (AMRadV). Penal provisions in § 95 set up to three years prison or a fine on the breach of § 7.

The German Medicinal Products Act contains instructions for SmPC, PIL and Labelling for RP (§§ 10, 11, 11a) that are in line with EU provisions. However, the German law does not adopt the minimum requirements for the vial (ref. Art. 66 (3) of Directive 2001/83/EC). In contrast, the same rules for the labelling of primary packaging as for conventional medicinal products apply completed by additional requirements laid down in AMRadV.

The need for manufacturing license and exemptions thereof are described in § 13. According to § 13 (1) 2nd sentence public pharmacies and hospital pharmacies would need a manufacturing license for preparing RP while general manufacturing activities in pharmacies were exempted from this requirement. The German legislators obviously did not consider the preparation of RP as normal pharmacy business. The § 13 (2b) of German Medicines Act opens the possibility for a physician to manufacture medicinal products under his responsibility and for use with his/her patients.

Educational requirements for a “Qualified Person” (QP) are given in § 15. According to sub-section 3 QPs for RP need a diploma in science or medicine and 3 years of practical experience in nuclear medicine or radiopharmaceutical chemistry. For comparison, QPs for conventional medicinal products need a license to practice as a pharmacist or post-graduate education equal to pharmacy studies and two years of practical experience in the quality control of medicinal products.

It is noteworthy that the distribution channel for RP may by-pass pharmacies as laid down in § 47 (1) 2. f (“Vertriebsweg”). They may be delivered directly to hospitals and physicians by wholesalers and pharmaceutical entrepreneurs.

To complete, a number of sections deal with the fact that in case of RP and in contrast to conventional medicinal products, the Ministry of Health may only issue ordinances in agreement with the Ministry for the Environment, Nature Conservation and Nuclear Safety (§§ 7, 12, 26, 35, 36, 45, 46, 48, 54, 67a, 74 and 79).

Table 2: Relevant sections of the German Medicinal Products Act related to RP

Source	Text	Meaning
§ 4 (1)	*Finished medicinal products are medicinal products which are manufactured beforehand and placed on the market in packaging intended for distribution to the consumer or other medicinal products intended for distribution to the consumer, in the preparation of which any form of industrial process is used or medicinal products which are produced commercially, except in pharmacies. Finished medicinal products are not intermediate products intended for further processing by a manufacturer.*	Definition of the term "finished product"
§ 4 (8)	*Radiopharmaceuticals are medicinal products which are or contain radioactive substances and spontaneously emit ionizing radiation and which are intended to be used on account of these properties; radionuclides (precursors) which have been manufactured for the radiolabeling of other substances prior to administration as well as systems with a fixed mother radionuclide which forms a daughter radionuclide (generators) shall also be regarded as radiopharmaceuticals.*	Definition of the term "RP"
§ 4 (17)	*Marketing is the keeping in stock for sale or for other forms of supply, the exhibiting and offering for sale and the distribution to others.*	Definition of "marketing"
§ 4 (31)	*Reconstitution of a finished medicinal product for human use is the conversion of the medicinal product into its usable form immediately prior to its use according to the specifications contained in the package leaflet or, within the framework of the clinical trial in accordance with the trial protocol.*	Definition or the term "Reconstitution"
§ 7	*Radiopharmaceuticals and medicinal products treated with ionizing radiation* *(1) It shall be forbidden for radiopharmaceuticals or medicinal products in the manufacture of which ionizing radiation has been used to be placed on the market unless the authorisation to do so has been given by ordinance according to sub-section 2.* *(2) The Federal Ministry is hereby empowered to authorize, in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, by means of an ordinance subject to the approval of the Bundesrat, the placing of radiopharmaceuticals on the market or the use of ionizing radiation in the manufacture of medicinal products in so far as this is deemed, according to the current level of scientific knowledge, to be justified for medicinal purposes and in so far as it does not compromise human or animal health. The ordinance may prescribe the channel for distribution for the medicinal products and specify that certain data concerning their radioactivity are to appear on the container, the outer packaging and the package leaflet. The ordinance shall be issued by the Federal Ministry of Consumer Protection, Food and Agriculture in agreement with the Federal Ministry and the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, in so far as medicinal products intended for administration to animals are concerned.*	Prohibition of placing on the market of RP and medicinal products treated with ionizing radiation
§ 11	*(2a) In the case of radiopharmaceuticals, sub-section 1 shall apply mutatis mutandis with the proviso that the precautions which are to be taken by the user and the patient in the preparation and administration of the medicinal product, as well as special precautions for the disposal of the containers used for transport and for the disposal of medicinal products which are not used, are taken.*	Special requirements for PIL
§ 11a	*(1b) In respect of radiopharmaceuticals, details of the internal radiation dosimetry, additional detailed instructions for the extemporaneous preparation and the quality control of this preparation shall also be given and, where necessary, the maximum storage time shall also be indicated during which an intermediate preparation, such as an eluate or the medicinal product when ready for use, corresponds to its specifications.*	Special requirements for SmPC

§12	*(2) […] The ordinance pursuant to sub-section 1, 1a or 1b shall be issued in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety in the case of radiopharmaceuticals and medicinal products in the manufacture of which ionizing radiation is used […].*	Empowerment in respect of labelling, package leaflet and package sizes
§ 13	*(1) […]* *(2) The following shall not require an authorisation pursuant to sub-section 1:* *1. the owner of a pharmacy manufacturing medicinal products within the scope of the normal operation of a pharmacy, reconstituting or packaging including the labelling of medicinal products intended for clinical trials in so far as this corresponds to the trial protocol,* *2. the body responsible for a hospital, in so far as it is authorised to distribute medicinal products pursuant to the Law on Pharmacies, reconstituting or packaging including the labelling of medicinal products intended for clinical trials in so far as this corresponds to the trial protocol,* *[…]* *The exceptions specified in sentence 1 shall not apply to the manufacture of […] radiopharmaceuticals.* *[…]* *(2b) Furthermore, an authorisation pursuant to sub-section 1 shall not be required by a person who is a physician or otherwise authorised to practise medicine on humans in so far as the medicinal products are manufactured directly under his/her professional responsibility for personal use by a specific patient. Sentence 1 shall not apply to:* *[…]* *2. medicinal products intended for clinical trials in so far as it is not merely a case of reconstitution.*	Manufacturing license and exemption for pharmacies, hospitals and physicians
§ 15	*(1) Proof of the required expert knowledge on the part of the qualified person […] shall be furnished by:* *1. the license to practise as a pharmacist, or* *2. the diploma in pharmacy, chemistry, biology, human or veterinary medicine attained upon completion of university studies as well as a period of at least two years' practical experience in the field of qualitative and quantitative analysis and other quality testing of medicinal products.* *(2) In the cases specified in sub-section 1 number 2, proof shall be furnished […] that the university studies comprised theoretical and practical instruction at least in the following basic subjects […].* *(3a) Sub-section 2 shall not apply to the manufacturing and testing of […] radiopharmaceuticals […]. In place of the practical experience required in sub-section 1, proof must be furnished of:* *[…]* *5. in the case of radiopharmaceuticals at least three years' experience in the field of nuclear medicine or that of radiopharmaceutical chemistry […].*	Expert knowledge of Qualified Person for RP
§ 22	*[...] (3b) In the case of radiopharmaceuticals which are generators, a general description of the system, including a detailed description of those components of the system which are able to influence the composition or quality of the secondary radioactive nuclide preparation, as well as the particular qualitative and quantitative characteristics of the eluate or the sublimate, are to be provided.*	Dossier requirements
§ 26	*(1) After consultation with experts from the fields of medical and pharmaceutical science and practice and with the approval of the Bundesrat, the Federal Ministry be empowered to regulate by ordinance the requirements for the information, documents and expert opinions specified in Sections 22 to 24, also in conjunction with Section 38 sub-section 2, as well as for their examination by the competent higher federal authority. The regulations must comply with the prevailing state of scientific knowledge and are to be continually adjusted to it; animal experiments, in particular, shall be replaced by other test methods if this is reasonable in the light of the*	Guidelines for the testing of medicinal products

	state of scientific knowledge and considering the purpose of the test. The ordinance shall be issued, in so far as radiopharmaceuticals and medicinal products in the manufacture of which ionizing radiation is used are concerned, and in so far as tests for ecotoxicity are concerned, in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety […].	
§ 35	*[…] (2) The ordinances, pursuant to sub-section 1 numbers 2 to 4, shall be issued in agreement with the Federal Ministry for Economics and Technology and, in the case of radiopharmaceuticals and medicinal products in the manufacture of which ionizing radiation is used, in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety […].*	Empowerments in respect of marketing authorisation and exemptions
§ 36	*[…] (3) The ordinance pursuant to sub-section 1 shall be promulgated in agreement with the Federal Ministry for Economics and Technology and, in the case of radiopharmaceuticals and medicinal products in the manufacture of which ionizing radiation is used, in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety […].*	Empowerment in respect of standard marketing authorisations
§ 45	*[…] (3) The ordinance shall be issued in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, in so far as radiopharmaceuticals and medicinal products in the manufacture of which ionizing radiation is used are concerned.*	Authority to allow further exceptions to the pharmacy-only requirement
§ 46	*[…] (3) The ordinance shall be issued in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, in so far as radiopharmaceuticals and medicinal products in the manufacture of which ionizing radiation is used are concerned.*	Authority to extend the pharmacy-only requirement
§ 47	*(1) Pharmaceutical entrepreneurs and wholesalers may only supply medicinal products reserved for pharmacies to the following parties other than pharmacies* *1.) other pharmaceutical entrepreneurs and wholesalers,* *2.) hospitals and physicians as far as the following items are concerned:* *[…]* *f) radiopharmaceuticals*	Distribution channel: RP can be sold directly to hospitals and physicians, by-passing pharmacies
§ 48	*[…] (5) The ordinance shall be issued in agreement with the Ministry of the Environment, Nature Conservation and Nuclear Safety in the case of radiopharmaceuticals or medicinal products the manufacturing process of which uses ionising radiation.*	Prescription requirement
§ 54	*(1) The Federal Ministry is hereby empowered to issue in agreement with the Federal Ministry for Economics and Technology, by ordinance subject to the approval of the Bundesrat, internal regulations for enterprises or facilities which bring medicinal products into the purview of the present Act or in which medicinal products are developed, manufactured, tested, stored, packaged or placed on the market, in so far as it is deemed necessary in order to ensure the proper operation of the enterprise or facility and the quality required of the medicinal products; this shall apply mutatis mutandis to active substances and other substances as well as tissues intended for the manufacture of medicinal products. […] The ordinance shall be issued in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety if radiopharmaceuticals or medicinal products in the manufacture of which ionizing radiation is used are concerned. […]*	Internal regulations
§ 64	*[…] (2) Persons in charge of supervision shall carry out this activity as their main profession. The competent authority may call in experts. In so far as blood preparations, tissues and tissue preparations, radiopharmaceuticals, […] are concerned, the competent authority shall summon members of the competent higher federal authority to participate as experts. […]*	Conducting supervision
§ 67a	*[…] (4) The ordinance pursuant to sub-section 3 shall be promulgated in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety in the case of radiopharmaceuticals or medicinal products in the manufacture of which ionizing radiation is used.*	Database supported information system

§ 74	*[…] (2) The Federal Ministry for Finance shall settle the details of the procedure indicated in subsection 1, in agreement with the Federal Ministry, by ordinance […].* *The ordinance shall be issued in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, as far as radiopharmaceuticals and active substances or medicinal products and active substances in the manufacture of which ionizing radiation is used are concerned […].*	Participation in custom offices
§ 79	*(1) The Federal Ministry is hereby empowered to permit exceptions to the regulations laid down by the present Act and by the ordinances issued by virtue of the present Act, in agreement with the Federal Ministry of Economics and Technology, by ordinance not subject to the approval of the Bundesrat, if the necessary supply of medicinal products to the population would otherwise be seriously jeopardized and if a direct or indirect hazard by medicinal products to human health is not to be feared; in particular, regulations can be adopted to counter the spread of risks that might occur in reaction to the presumed or confirmed spread of pathogenic substances, toxins, chemicals or exposure to ionising radiation.* *(2) The Federal Ministry of Agriculture, Food and Consumer Protection is hereby empowered to permit exceptions to the provisions contained in the present Act and the ordinances issued on the basis of the present Act, in agreement with the Federal Ministry and the Federal Ministry of Economics and Technology, by ordinance not subject to the approval of the Bundesrat, if the necessary supply of medicinal products to livestock would otherwise be seriously jeopardised and if a direct or indirect hazard by medicinal products to human or animal health is not to be feared.* *(3) The ordinances pursuant to sub-section 1 or 2 shall be issued in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, in so far as radiopharmaceuticals and medicinal products in the manufacture of which ionising radiation is used or regulations to protect against the risks of ionising radiation are concerned.* *(4) The term of validity of the ordinance pursuant to sub-section 1 or 2 shall be limited to six months.* *(5) In the event of a shortage of medicinal products necessary for the prevention or treatment of life-threatening diseases in the population, the competent authorities may permit, on a case-by-case basis, the temporary placing on the market as well as, by way of derogation from Section 73 sub-section 1, the import and introduction of medicinal products which are not authorised for placing on the market or registered for trade within the purview of this Act if they may be placed on the market in the State from which they are being introduced into the purview of the present Act. The granting of permission by the competent authority also counts as an attestation pursuant to Section 72a sub-section 1 sentence 1 number 3 or pursuant to Section 72b sub-section 2 sentence 1 number 3, that the import is in the public interest. The existence of a shortage within the meaning of this sub-section, as well as its cessation will be declared by the Federal Ministry by way of publication either in the Federal Gazette or in the electronic Federal Gazette. The publication shall be issued in agreement with the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, in so far as radiopharmaceuticals and medicinal products in the manufacture of which ionising radiation is used are concerned.*	Authority to permit exceptions in times of crisis
§ 95	*Any person who* *[…]* *3. places radiopharmaceuticals and medicinal products in the manufacture of which ionizing radiation is used on the market, in breach of Section 7 sub-section 1,* *[…]* *shall be liable to imprisonment for a term not exceeding three years or to a fine.*	Penal provisions

3.2.3 15th amendment of the German Medicinal Products Act in 2009

A number of changes have been introduced into the German Medicinal Products Act in July 2009 that had a strong impact on nuclear medicine and RP. The 15th amendment has limited the legal ways of manufacturing and using RP dramatically by deleting § 4a (3) from the law. This section exempted all medicinal products that were produced by or under the responsibility of a physician for administration to his patients from the scope of the Act. Nuclear medicine physicians made wide use of the § 4a (3) AMG and consequently there was the fear of a shortage in patient supply following the law change *(DGN, 2009*). As a compensation § 13 (2b) was introduced into the law (rf. Table 2). According to this section a physician does not need a manufacturing license if "*the medicinal products are manufactured directly under his/her professional responsibility for personal use by a specific patient*". However, as the Medicinal Products Act applies, the physician is obliged to inform his supervisory authority about those manufacturing activities (§ 67 AMG "Anzeigepflicht"). The manufacturing has to be done according to state-of-the-art pharmaceutical standards, i.e. the European Pharmacopoeia, if monographs are available. However, the question if the EU-GMP-guideline had to be applied for manufacturing activities under § 13 (2b) AMG needed interpretation. A Votum of the GMP-inspectors in 2009 did not clarify the situation as it referenced not only to the monographs and general chapters of the Ph.Eur., but also to Annex 1 and Annex 3 of the EU-GMP-guideline and the PIC/S-guide PE010-03 *(EFG Votum V12001, 2009).* A clear statement on the applicability of the EU-GMP-guideline was given in 2011 in the "Aide Mémoire on the supervision of PET-radiopharmaceutical production" *(ZLG, 2011).* However, as the supervision of the Medicinal Products Act is in the competency of the Federal States, the interpretation of the law may still differ among the regions. The transitional period for the deletion of § 4a (3) AMG has expired only in August 2011 and it has to be observed how GMP-inspectors will deal with the § 13 (2b) AMG provisions in future.

In 2006 *Schirbel* noted that kits are "finished products" (Fertigarzneimittel) and for the assembling of the drug product according to the instructions of the marketing authorisation holder, a nuclear medicine department would not require a manufacturing license acc. to § 13 AMG. This has changed since the 15th amendment introduced the term "reconstitution" into the law (§ 4 (31) AMG). Only the "reconstitution" of a medicinal product is exempted from the need for a manufacturing license. It was clarified by the Federal Ministry of Health, that "reconstitution" means adding something that has originally been part of the medicinal product and has been removed (e.g. water from a lyophilized powder). Consequently, the labelling of a carrier molecule with a radionuclide is not "reconstitution". The extemporaneous preparation of RP from authorised kits following manufacturer's instructions can be done in accordance with § 13 (2b) AMG or according to AMRadV.

3.2.4 The Ordinance of Radioactive Pharmaceuticals or Pharmaceuticals treated with Ionizing Radiation (AmRadV)

Based on § 7 AMG Germany has an ordinance dealing exclusively with RP and medicinal products treated with ionizing radiation during manufacture. The ordinance came into force in 1987 and consists today of 6 Articles. Article 1 is dedicated to medicinal products treated with ionising radiation while Article 2 specifies the conditions for marketing of RP. According to the first sentence they can be authorised for marketing by the competent authority in compliance with § 21 AMG and some exemptions of § 21 (2) AMG apply. Namely the exemptions Nr. 1a) "autologous preparations with material of human origin", 1b) "pharmacy preparation of cytostatics, parenteral nutritions, or other medically justified cases from authorised medicinal products", 1c) "specific provisions for treating of infectious diseases", 2) "clinical trial in humans", 5) "clinical trial in animals" and 6) "compassionate use" apply. Notably, RP are not comprised under the provisions of § 21 (2) Nr. 1 AMG ("Defektur", pharmacy preparation up to 100 pieces per day)" *(Schweim, 2011)*. Sub-section 1b) "medically justified preparation from authorised products" would be suitable for extemporaneous preparations. However, the emergency character of this provision ("if there is no other product with marketing authorisation available") is in contrast to the normal application of an authorised medicinal product.

Furthermore, according to AMRadV certain medicinal products that contain traces of natural radioactivity may be marketed without authorisation.

Wide use is made from provisions in the second sentence of section 2 especially after the 15th amendment of the AMG. RP are exempted from the prohibition of § 7 AMG if they are

1. provided to diagnose the nature, state or functions of the body
2. manufactured in a clinical institution on the basis of a manufacturing license acc. to § 13 AMG, and
3. administered in said institution to not more than 20 patients per week in accordance with state-of-the-art medical science and on the basis of a patient-specific medical prescription.

Although this exemption seems to give explicitly clear instructions, it still leaves room for interpretation. What is meant by "clinical institution" (klinische Einrichtung)? This is not defined in the law. Why is the number of patients limited to 20 per week and not to 10 or 30? What about a group of hospitals with a radiopharmacy laboratory at one site, supplying the others with RP – is this still "one" clinical institution?

In the continuation of § 2 (1) 2nd sentence AMRadV the transformation of Article 7 of Directive 2001/83/EC is found:

A marketing authorisation is not required

for radioactive medicinal products that are prepared in a hospital pharmacy or hospital-supplying pharmacy exclusively on the basis of approved radionuclide generators, radionuclide kits or radionuclide precursors following the instructions of the pharmaceutical entrepreneur.

According to AMRadV solely the hospital pharmacy or hospital-supplying pharmacy is authorises as institution for the extemporaneous preparations of RP while according to § 13 (2) AMG they would have to apply for a manufacturing license for it.
Article 3 of the AMRadV gives additional provisions for SmPC, PIL and labelling of radioactive medicinal products. Article 4 clarifies the relationship to Ordinances on Radiation Protection and on Roentgen Examinations. Articles 5-9 are penal and transitional provisions as well as out-dated articles.

3.2.5 Investigational RP for clinical trials in DE

In-line with the Directive 2001/20/EC, the "Ordinance on applying Good Clinical Practice when performing Clinical Trials with Medicinal Products for Human Use" (Verordnung über die Anwendung der guten klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen, GCP-V) does not contain exemptions for RP. Any institution or person aiming for clinical trials has to manufacture the IMP according to GMP and has to be in possession of a manufacturing license according to § 13 AMG *(GCP-V, Meller, 2012).* A clinical trial application with RP has to be approved not only by the local ethics committee and the BfArM but also by the Bundesamt für Strahlenschutz (Federal Office for Radiation Protection; BfS). At BfS timelines for the assessment of applications or implicit approval are not established. Recently some changes have been introduced for trial medication.[3] However, the simplifications do not apply to RP under development as the diagnostic or therapeutic principle.

3.2.6 Summary

The legal situation in Germany is complex and hardly comprehensible: a RP may be produced under § 13 (2b) AMG without manufacturing license, but if the same product shall be used in a clinical trial, a manufacturing license is indispensable *(GCP-V; Meller, 2012; DGN, 2009).* In some Federal States physicians may employ a third party to manufacture RP under their responsibility according to § 13 (2b) AMG while authorities of other states insist on the personal presence of the physician at the site of production. A product may be prepared in a hospital for in-house use according to § 2 (1) 2nd sentence AMRadV while a commercial PET manufacturer in the neighbourhood would need a MA in order to supply the same product to the hospital. Hospital pharmacies are the only establishments authorised literally for the extemporaneous preparation of RP from kits and precursors according to AMRadV, while § 13 (2) AMG obliges them to acquire a manufacturing license. An overview is given in Table 3.

[3] Verordnung zur Änderung strahlenschutzrechtlicher Verordnungen vom 04. Oktober 2011; Bundesgesetzblatt I S. 2000, vom 13. Oktober 2011

Table 3: Overview of routes of manufacturing or marketing of RP for administration to patients compliant with German law

Legal basis	Usable by?	Manufacturing license required? ("Full GMP")	Placing on the market? (=sell to third parties)	Product example
MA acc. to § 21 AMG in combination with § 2 (1) 1st sentence AMRadV	Pharmaceutical company; public or private institutions, hospitals, physicians etc. (all legal entities that are possible MAHs)	Yes	Yes	^{18}F-FDG solution for injection
§ 13 (2b) AMG	Physician	No (but: notification of supervisory authority, acc. to § 67 AMG)	No	Authorised and non-authorised RP for both diagnostic and therapeutic purposes including kit-based RP
Clinical trial acc. to § 21 AMG in combination with § 2 AMRadV and GCP-V	Commercial sponsor or academic investigator	Yes (manufacturing license for IMP)	(Yes, with the limitations applicable to medicinal products in clinical investigation)	New molecular entities as well as well-known substances
§ 2 (1) 2nd sentence AMRadV (diagnostic products, manufacturing license, not more than 20 patients per week)	Clinical institution	Yes	No	Authorised and non-authorised diagnostic RP (^{11}C-, ^{18}F-, ^{99m}Tc-, ^{68}Ga-labelled compounds)
§ 2 (1) 3rd sentence AMRadV (RP made from authorised generators, precursors and kits in hospital pharmacy-> transformation of Art. 7 of Dir 2001/83/EC)	Hospital pharmacy	No(?) ("magistral" preparation in hospital pharmacy or § 13 (2) AMG?)	No	Kit-based products with MA: ^{99m}Tc-kits; ^{90}Y-Zevalin; ^{111}In-Octreoscan

3.3 United Kingdom (UK)

3.3.1 General description

Great Britain was among the first countries in Europe considering radiopharmaceuticals as medicinal products already in the 1960s *(Cortès-Blanco 2003).* The changes in national law forced by Directive 89/343/EEC related therefore only to "radiopharmaceuticals-associated products" –"a generator, kit or precursor which is not itself a medicinal product". These changes were introduced by *The Medicines Act 1968 (Applications to Radiopharmaceuticals-associated Products) Regulations1992.*

Nowadays, the landscape in UK consists of approximately 100 radiopharmacy departments that are nearly all based in hospitals. 95 % are part of the National Health System (NHS) and 5 % are commercial. Together they serve approximately 200 nuclear medicine departments. The concept of a "centralized radiopharmacy practice" is well established, although the number of nuclear medicine departments supplied by each individual radiopharmacy differs largely (Table 4). 74 % of the radiopharmacies serve less than five departments while only 8 % serve 10 or more. The centralized radiopharmacy units are predominantly run by responsible radiopharmacists while only a few small units are still run by physicists. Today "full" GMP compliance is required for the preparation of RP as for all other pharmaceutical production activities. Strong support to the field is given by the UK radiopharmacy group. *(Decristoforo, talk, 2006; Mather, talk, 2007; ARSAC, 2010)* For education, post-graduate courses in Radiopharmacy have been established from the 1980s; however, it is not a mandatory requirement for persons working with RP. The Medicines and Healthcare Products Regulatory Agency (MHRA) is competent for granting both manufacturing licenses and marketing authorisations.

Table 4: Central radiopharmacies in the UK *(adopted from ARSAC 2010)*

Central radiopharmacy supplying	Percentage (%)
< 5 sites	74
5 – 9 sites	18
10 sites or more	8

3.3.2 UK legislation regarding medicinal products

"The current body of UK medicines legislation comprises the Medicines Act 1968 and approximately 200 statutory instruments. It has developed piecemeal since the Medicines Act 1968 came into force some 40 years ago." *(Project to consolidate and review UK*

medicines legislation; www.mhra.gov.uk; last visited on 1st April 2012) A project is underway to consolidate and simplify the law regulating medicines in the UK resulting in *The Human Medicines Regulations* which is due to come into force in July 2012. For the time being the central documents in British national law regarding medicinal products are still *The Medicines Act 1968* and *The Medicines for Human Use (Marketing Authorisations etc.) Regulations 1994.* Their provisions "apply to the sale, supply and manufacture of all radiopharmaceuticals" and "[…] are enforced by the Medicines and Healthcare products Regulatory Agency (MHRA) in Great Britain and the Department of Health, Social Services and Public Safety (DHSSPS) in Northern Ireland." *(ARSAC, 2010).* Part II of The Medicines Act 1968 deals with "Licenses and certificates relating to medicinal products". Section 8 sets "provisions as to manufacture and wholesale dealing", clearly stating that any "manufacture or assemble" of a medicinal product requires a license. In section 10 of the Act the exemptions for pharmacies with regard to manufacturing license in accordance with Article 3 of Directive 2001/83/EC can be found:

[…] the restrictions imposed by sections 7 and 8 of this Act do not apply to anything which is done in a registered pharmacy, a hospital, a care home service or a health centre and is done there by or under the supervision of a pharmacist and consists of
a) preparing or dispensing a medicinal product in accordance with a prescription given by a practitioner
b) assembling a medicinal product provided that the assembling takes place in a registered pharmacy […]"

The *Medicines for Human Use (Marketing Authorisations etc.) Regulations 1994* came into force on 1st of January 1995. According to Schedule I, exempted from the requirement of MA is: e.g. anything done by a doctor or dentist with relation to a medicinal product prepared for administration to his patients or anything done in a registered pharmacy under the supervision of a pharmacist. Furthermore, "a relevant medicinal product which is supplied to fill a special need and in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients on his direct responsibility" is exempted from the need for MA *(MHRA Guidance No. 14 – unlicensed specials)*.

The first sub-paragraph of section 5 is the transformation of Article 7 of Directive 2001/83/EC:

5. (1) Regulations 3(1) shall not apply to a radiopharmaceutical for human use
(a) which is prepared at the time at which it is intended to be administered; and
(b) which is prepared, in accordance with the manufacturer's instructions and by the person by whom it is to be administered, exclusively from a kit, generator or precursor (or from more than one of these) in respect of which a marketing authorisation is in force; and
(c) the administration of which is not or will not be a contravention of regulation 2 of the Medicines (Administration of Radioactive Substances) Regulations 1978.

The second sub-paragraph contains the definition of RP in UK:

(2) In this paragraph
"generator" means any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be removed by elution or by any other method and is to be used in a radiopharmaceutical;
"kit" means any preparation to be reconstituted or combined with radionuclides in a final radiopharmaceutical usually prior to its administration;
"precursor" means a radionuclide produced for the radio-labelling of another substance prior to its administration, other than a radionuclide which is incorporated in or produced from a generator or is included in a radiopharmaceutical;
"radiopharmaceutical" means any relevant medicinal product which when ready for use contains one or more radionuclides included for a medicinal purpose.

The definition is almost identical to the one given in Directive 2001/83/EC, as amended. Only the wording for "precursor" is slightly different, clarifying that the radionuclide incorporated in or produced by a generator is not meant by the term. According to the first sub-paragraph point (b) the RP must be prepared "by the person by whom it is to be administered" (i.e. a physician). However, this does not explain the legal basis for the radiopharmacies performing extemporaneous preparations without MA. The possible ways to supply third parties are to be registered as a pharmacy and use the Section 10 exemption or to operate under a Special's License *(Mather, talk, 2007).*
The current review of the legislation will not result in a change of these points. A "request for consultation" of the MHRA regarding the "review of medicines legislation" lists 28 exemptions for "sale, supply and administration of medicines" and none of relevance for this thesis shall be abandoned *(MHRA, 2010).*

3.3.2. Radiopharmacy units operating under Section 10 exemptions

Radiopharmacies operating under the section 10 exemptions are registered pharmacies according to section 74 of The Medicines Act 1968. In such "radiopharmacies […] RP are prepared under the supervision of a pharmacist and compliance with the principles of GMP is audited according to EL (97)52[4] by an approved pharmacy Regional Quality Assurance Specialist." *(BNMS Radiopharmaceutical Science Group and UK Radiopharmacy Group, 2012)*. Within such a unit, "the Chief Pharmacist[5] has overall responsibility for the service and a Pharmacist must release any product for clinical use. […] The Accountable Pharmacist is responsible for all aspects of the radiopharmacy service including the approval of all systems of work and documentation. […] This person is also an Authorised Pharmacist […] designated to supervise the aseptic process and release of products for use. An Authorised Pharmacist should be in the department and be in a position to intervene at any part of the

[4] NHS Executive Letter (97) 52: Aseptic Dispensing in NHS Hospitals. London: Department of Health, 1997

[5] Chief Pharmacists are ultimately responsible for the „safe and secure handling of medicines" in the NHS Healthcare Trust they are employed with (www.nhs.uk)

radiopharmaceutical preparation process" *(BNMS Radiopharmaceutical Science Group and UK Radiopharmacy Group, 2012)*.

3.3.3. Radiopharmacy units operating with a Specials' license

Although "in the interest of public health the exemption is narrowly drawn" *(MHRA Guidance No. 14)* frequent use is made of the Specials' license provision for the extemporaneous preparation of RP. For units operating with a Specials' license, the following conditions apply: "There is a bona fide unsolicited order, the product is formulated in accordance with the requirement of a doctor or dentist registered in the UK, and the product is for use by their individual patients on their direct personal responsibility. If a 'special' is manufactured in the UK, the manufacturer must hold a manufacturer's (specials) licence issued by the MHRA. A 'special' may not be advertised and may not be supplied if an equivalent licensed product is available which would meet the patient's needs. Essential records must be kept and serious adverse drug reactions reported to the MHRA." *(MHRA website: medicines that do not need a license, last visited on 5th February 2012).*

One of the requirements for Specials' license is a manufacturing license issued by MHRA. As a consequence, "radiopharmacies that operate under a Manufacturer's Specials' License are audited for compliance with the principles of GMP by the" MHRA *(BNMS Radiopharmaceutical Science Group and UK Radiopharmacy Group, 2012)* Within the unit, "there must be a named person responsible for production and a different independent person responsible for Quality Control." *(BNMS Radiopharmaceutical Science Group and UK Radiopharmacy Group, 2012).* In most cases at least one person "would be a pharmacist" *(Mather, talk, 2007)*

3.3.4 Recent developments

Despite all attempts of creating tailored laws and regulations the special nature of RP and the specific problems in commercialisation cause also some open issues in UK. Indicative are the following publications of the UK Radiopharmacy Group and the NHS Pharmacy QA Committee: "Advice for Nuclear Medicine Departments following discontinuation of licensed radiopharmaceuticals and kits from the home market" (2009) and "Responsibilities of Chief Pharmacist for the purchase and supply of radiopharmaceuticals" (2009). In case of market discontinuation measures such as import of products authorised outside UK in accordance with the Specials' license are promoted. Regarding the responsibility of the Chief Pharmacist there is to be differentiated between the following cases:

1. If RP are manufactured in a Specials' licensed unit with no pharmacy input, it is advised to close a formal contract "defining standards and responsibilities" and enabling the Chief Pharmacist to receive "a copy of each MHRA report" of the facility.

2. “In a section 10 Unit the ultimate responsibility rests with the Chief Pharmacist.” He should “performance manage the supervising pharmacist and would be responsible for compliance with guidelines”.
3. “In the situation of a Nuclear medicine department receiving multi-dose vials from an outside supplier the responsibility of the Chief Pharmacist cannot be devolved. […] he must be satisfied that the Nuclear medicine department is carrying out processes to the appropriate standards […].”

(UK Radiopharmacy Group and NHS Pharmacy QA Committee, 2009)

Due to the shortage of ^{99m}Tc-generators in the last years new questions arose such as if a used generator could be handed over to another hospital under the Specials’ License or if an unlicensed radiopharmacy could supply another with multidose vials of generator eluate. It is predominantly the question of liability in case of product defects that stands behind all concerns *(ARSAC, 2010).*

3.3.5. Investigational RP for clinical trials in the UK

The relevant document transforming Directive 2001/20/EC into national law is *The Medicines for Human Use (Clinical Trials) Regulation 2004 as amended [SI 2004 1031]*. “In UK there are only a few units authorised for manufacturing of RP for clinical trials. In accordance with EU law the manufacture of RP as an investigational medicinal product (IMP) requires a manufacturing license and a QP release. Neither the “section 10 exemption” nor the “preparation under specials’ license” apply to this specific condition” *(Mather, talk, 2007).* In UK the QP responsible for the release of the IMP has to be named on the IMP license. For RP outside clinical trials, manufactured in “radiopharmacies that operate either under a Manufacturer’s License or under Section 10 of the Medicines Act, there is currently no requirement for […] a Qualified Person (QP).” *(BNMS Radiopharmaceutical Science Group and UK Radiopharmacy Group, 2012).*

The exemptions of section 37 of the clinical trials legislation regarding “assembling” of an IMP do not apply to kit-based RP as “assembling” is regarded as “packaging and labelling and not [.] the preparation of medicines from their ingredients” *(Good Manufacturing Practice: Investigational Medicinal Products (IMP) FAQs Nr. 4; www.mhra.gov.uk; last visited on 1st April 2012).*

3.4 France (FR)

3.4.1 General description

The production of RP in France - as for all other medicinal products – strictly requires supervision by a pharmacist who is taking over the responsibility ("monopole de pharmacien"). France transformed the Directive 89/343/EEC into national law by means of "Loi n°92-1279 du 8 décembre 1992" amending the cod e of public health ("Code de la santé publique", CSP). Subsequently, the commercial manufacturers of RP were regarded as Pharmaceutical Establishments ("établissement pharmaceutiques") and the extemporaneous preparation had to take place in pharmacies. The Code differentiates between public pharmacies ("officines") and pharmacies for internal use/service ("pharmacie à l'usage intérieur", PUI), such as hospital pharmacies. In the year 2000 and with the "Décret n°2000-1316 du 26 décembre 2000", the mission of PUI was extended to RP *(Edet, talk, 2010)* while public pharmacies may not prepare RP.

Approximately 200 radiopharmacy units exist in France and about 70 % of them employ at least one radiopharmacist. "Radiopharmacie" is a specialisation of pharmacists, they can acquire either by postgraduate studies in radiopharmacy or three years of practical experience in manufacturing and control of RP. The details are laid down in "Arrêté du 1er décembre 2003" on the qualification of pharmacists using RP. 200 nuclear medicine centres exist in France, equipped with 400 gamma cameras and 70 PET-scanners. Approximately 20 cyclotrons for medical use are operated, most of them run by private, commercially operating institutions *(Edet, talk, 2010)*.

In 2008 the National Union of Radiopharmacists (Syndicat National des Radiopharmaciens) and the French Society for Radiopharmacy (Société française de radiopharmacie) have published a dossier summarizing the relevant texts for preparing radiopharmaceuticals in France ("RADIOPHARMACIE: Bonnes pratiques & Guidelines"), including both small-scale preparation ("préparation") and industrial manufacturing ("fabrication"). The national competent authority both for granting MA and manufacturing licenses in France is the Agence Française de la Securité Sanitaire des Produits de la Santé (AFSSAPS).[6] It issues best practice guides for officines, PUI, hospitals and industry.

[6] Currently under reorganisation to "Agence nationale de sécurité du médicament et des produits de santé" (ANSM; National Agency for Medicinal and Health Product Safety); due 1st August 2012

3.4.2 The Code of Public Health (Code de la Santé Publique, CSP)

The Code of Public Health is the central document in French health law. The definitions of RP are laid down in Article L5121-1 CSP as an almost literal translation of the corresponding definitions of Directive 2001/83/EC, as amended. Other Articles of relevance for RP are: Article L5121-8 clarifying that every pharmaceutical speciality that is prepared industrially – also generators, precursors and kits – has to obtain a marketing authorisation of the AFSSAPS unless authorised by the European Union. Notably, the French law explicitly lists "generators, kits and precursors" in addition to the term "medicinal products". The exemptions for pharmacies to prepare medicinal products without MA are transformed into French law by Articles L5125-1 and L5126-2 CSP. According to Article L5125-1, "Officine" (public pharmacy) is an "establishment occupied with the retail dispensing of medicinal products" and "the execution of magistral and officinal preparations". They may, under certain conditions, outsource preparations to another officine or an authorised pharmaceutical establishment. However, "the preparation of radiopharmaceuticals is forbidden" for officines (Article L5125-1-1 and Article L5121-1 N°7) and instead included in the mission of "pharmacies à l'usage intérieur" (PUI). Article R5121-22 gives additional provisions for MA application for radionuclide generators and Article R5121-24 gives additional provisions with regard to the product information texts for RP as foreseen on EU level by Directive 2001/83/EC, as amended.

Important provisions are contained in Part IV of the CSP dealing with health care professionals, and in particular the Monopole of Pharmacist ("monopole de pharmacien"). Article L4211-1 states that the „preparation of medicinal products for human use" (sub-section 1) and the "preparation of generators, kits and precursors" (sub-section 3) is reserved for pharmacists, unless authorised in line with exemptions in the CSP. The French system differentiates between the pre-hospital and the hospital phase in the preparation of RP *(Edet, talk, 2010)*.

3.4.3 Pre-hospital preparation - Etablissements pharmaceutiques

Pre-hospital preparation of RP, as all other industrial manufacturing and wholesale trade of medicinal products, takes place in pharmaceutical establishments ("établissements pharmaceutiques"). As laid down in Article L5124 "the opening of a pharmaceutical establishment" is subjected to the need for an authorisation by AFSSAPS. At least one "responsible pharmacist" is required who must be part of the general management and, depending on the size of the enterprise, and can be assisted by additional "delegated pharmacists". Placing on the market of the products is subject to a MA issued by AFSSAPS or the European Commission.

3.4.4 Hospital preparation - Pharmacies à l'usage intérieur

The extemporaneous preparation of RP in line with Article 7 of Directive 2001/83/EC as well as hospital or magistral preparation of unauthorised RP takes place in PUI. "Healtcare establishments […], healthcare cooperation groups […], may dispose of one or more Pharmacies for internal use" (Article L5126-1). In general their activities are limited to the services for the sick persons within the establishment. They may only deliver medical products to other pharmacies in case those are not disposable (Article L5126-2) or in the case of certain medical research activities (Article L5126-1). However, they may deliver to other establishments (including free medicine practices organised in a network acc. to Article 6321-1) magistral and hospital preparations as well as reconstituted specialities. A PUI must be run by a pharmacist who is responsible for all pharmaceutical activities (Article L5126-5).
In order to prepare RP a PUI requires two types of authorisations: the authorisation for a PUI "to prepare radiopharmaceuticals" (Article R5126-9) which is given by the Regional Agency for Hospital Administration and the authorisation "for the use and storage of radionuclides […] for medical use or clinical research" (Article R1333-24 CSP) given by ASN. According to Article R5126-9, PUI are explicitly authorised to realise magistral or hospital preparations for other establishments or even free medical practices.
Guidance on the applicable quality standards for extemporaneous preparation is given by AFSSAPS: Good preparation practice – Chapter 9 radiopharmaceuticals *(AFSSAPS, Décision du 5 novembre 2007 - BPP).* "Only radiopharmacists, operating inside a PUI and having a written delegation of the leading pharmacist of the PUI may have the technical responsibility for the preparation and control of radiopharmaceuticals". *(AFSSAPS, Décision du 5 novembre 2007 – BPP)*. According to Article 5126-5 CSP "the pharmacist may be aided by other specialised personnel" (introduced by: Loi N°2002-73 du 17 janvier 2002).

3.4.5 Recent developments

There are some exemptions from the monopole of pharmacist that are important to understand some of the recent developments. The formation of economic interest groups ("groupements d'intérêt économiques", GIE) or healthcare cooperation groups ("groupements de cooperation sanitaires", GCS) according to Article L6133-1 CSP was initiated to foster development of services and collaboration between healthcare establishments, medico-social establishments and free physicians. These groups shall combine "administrative, logistic, technical, medical, educational or research activities" while not pursuing financial interests, although, according to Art. L6133-2, they may be constituted by public and private establishments including free practicing physicians. If the nature or volume of pharmaceutical activities in such a healthcare establishment does not justify the existence of a PUI […] storage and dispensing of medicinal products may be carried out under the responsibility of a medical doctor of the establishment (Article L5126-6). And,

“physicians in certain healthcare establishments without a PUI may for their professional use, order medicinal products from a pharmaceutical establishment or a officine” (Article R5126-114). As this applies also to RP they may by-pass radiopharmacies under such conditions. Moreover, recently a change of the “décret de compétence des manipulateurs d’électroradiologie médicale”, was proposed to authorise medical doctors to take over responsibility and supervision of the manufacturing of RP *(Hallouard, 2011).* Hallouard et al. conclude that “legally this proposal of modification would not have much chance to become valid as it is against the fundamentals of pharmaceutical law in France and in Europe”. In the eyes of the authors this would allow private or public institutions to construct a nuclear medicine service without a radiopharmacy unit and consequently a preparation or dispensing without responsible pharmacist.

3.4.7 Investigational RP for clinical trials in FR

One speciality to be noted with regard to clinical trials is Article L5126-11 CSP: “The pharmacist(s) of a health-care establishment (PUI) are authorised to realize in accordance with the pharmacopoeia, the preparations that are required for those experiments or trials.” Does this open the possibility for a compounding of RP from GMP-produced kits and precursors for clinical trials inside a PUI without the need for manufacturing license?

3.5 Spain (ES)

3.5.1 General description

In Spain, about 100 professionals work in the field, 50% - 65 % of them are pharmacists. "Radiopharmacy" is a recognized multidisciplinary speciality both for chemists and pharmacists. The education requires 3 years of hospital residency and a final exam with the goal of being responsible for a Radiopharmacy Unit *(SERFA, www.radiofarmacia.org, last visited on 19th March 2012).* However, only pharmacists can be responsible for release and dispensing of RP *(Decristoforo, talk, 2006; Dence, talk, 2008).*

The Spanish system is based more or less on "centralization" with two coexisting models: "hospital radiopharmacies" dealing with "extemporaneous preparation of kit-based RPs, blood-cell-labeling and compounding of PET-RPs exclusively for in-house use" and "commercial centralized radiopharmacies" providing "unit dose RPs to nearby hospitals and nuclear medicine centers" *(Peñuelas, talk, 2007).*

In 2006 Spain had "6 stand alone centralized radiopharmacies; 5-8 centralized hospital based radiopharmacies, 15-20 stand alone radiopharmacies and 5 centres producing and distribution FDG with marketing authorisation" *(Decristoforo, talk, 2006).*

A special regulation dedicated to RP existed from 1993 *(Real Decreto 479/1993, de 2 Abril regula los radiofármacos de uso humano*). It has been criticised for a long-time as "very ambiguous" and today parts of it are outdated. In addition, "the Spanish Pharmacopoeia has guidelines on RP procedures though they are not legally binding" *(Peñuelas, 2007)* but include instructions on the conduct of a Radiopharmacy Unit ("Unidad de Radiofarmacia") including radiopharmacies distributing to third parties (Radiofarmacia Distribuidora) *(AEMPS, www.aemps.gob.es, last visited on 17th March 2012)*.

Both MA and manufacturing licenses are granted by the Agencia Española des Medicamentos y Productos Sanitarios (AEMPS; Spanish Agency for Healthcare Products), while the authorisation of radiopharmacies is under the responsibility of the federal states in Spain *(SERFA, 2010).*

3.5.2 Legal basis: RD 479/1993 and RD 1345/2007

The legal frame for Radiopharmaceuticals in Spain is given by the Law on Medicines 25/1990, of 20th December, the Royal Decree 479/1993, of 2nd April, and the Royal Decree 1345/2007, of 11th October. In addition the legal measures on the protection against ionising radiation have to be followed (RD 1132/1990, of 14th September; RD 815/2001, of 13th July and RD 783/2001, of 6th July). Special provisions exist also for nuclear medicine centres (RD 1841/1997 of 5th December).

The central text on medicinal products in Spain, *Ley del Medicamento 25/1990 of 20th December* "considers in its chapter 4 RP as special medicinal products and establishes standards for manufacturing and extemporaneous preparation" *(SERFA, www.radiofarmacia.org, last visited on 19th March 2012).* As a result of this law and of the Directive 89/343/EEC in 1993 the Royal Decree 479/1993 was published in Spain "regulating radiopharmaceuticals for human use". The scope of this Royal Decree (RD) included the following products: "ready for use radiopharmaceuticals, generators, kits and precursors". These "industrially manufactured medicinal products are subject to previous authorization and registration by the Ministry of Health." However, this "authorization shall not be required for the extemporaneous preparation" of RP from "generators, kits and precursors duly authorized" *(RD 479/1993)*. GMP shall apply for the manufacture of ready for use RP completed by the rules laid down in Annex I of the Decree.

The prerequisites of extemporaneous preparations are as follows (Article 11):

a) request by a medical prescription
b) extemporaneous preparation in radiopharmacy unit by a qualified person under the supervision and control of an authorised expert in radiopharmacy
c) compliance with the principles of good extemporaneous preparation or radiopharmaceuticals as listed in Annex II.
d) given the special nature of these drugs, responsibilities for the proper use rest with the Head of the Radiopharmacy Unit […]

Annex II of the document gives instructions for the good practice of extemporaneous preparation according to the types of products that are manufactured. The overall responsibility of the Unit rests with the radiopharmacy expert.

Today most of the RD 479/1993 is out-dated – and the content of the respective sections is now included into RD 1345/2007. The definitions for RP, kits, generators and precursors are contained in Article 2, 22.-25., and do not differ from EU level. In addition a definition for extemporaneous preparation is given as follows

[…] a preparation at the moment of use of a registered radiopharmaceutical starting from radioisotopic labeling of a kit or autologous patient's own samples (cells, proteins), with a radionuclide or a radionuclide precursor produced by a generator, to obtain a ready for use radiopharmaceutical. This preparation may only be carried out upon medical prescription and under the principles of good extemporaneous preparation of radiopharmaceuticals […].

Section 3 of RD 1345/2007 deals with RP, namely Article 46 establishes the need for MA for "generators, kits and precursors as well as industrially manufactured RP". The following exemptions apply (Article 47):

a) extemporaneous preparation from authorised kits, generators or precursors, under supervision of a Radiopharmacy Expert and in an authorised Radiopharmacy Unit and for use in an authorised centre or institution
b) autologous cell preparations […]
c) PET radiopharmaceuticals prepared in an authorised Radiopharmacy Unit under supervision of a medical Radiopharmacy Expert if the following conditions are met:

- developed and used, for non-commercial purposes, in neighbouring centres of the national health system
- being substances in clinical investigation or being medicinal products that the AEMPS considers as satisfying quality, safety, efficacy, […] as well as being prepared in adequate conditions.

The scope of Radiopharmacy Units is "a) the preparation of ready-for-use RP, preparation of individual patients' doses, dispensing, dilution, reconstitution; b) extemporaneous preparation from precursors and kits or autologous cells and c) preparation of PET-radiopharmaceuticals" *(SERFA, 2010)*. They are authorised for "acquisition, reception, wholesale trade, preparation, quality control, documentation and dispensing of RP under the responsibility of a medical expert of Radiopharmacy" *(SERFA, 2010)*. They need an authorisation for the handling of radioactive substances granted by the Council for Nuclear Safety (Consejo de Seguridad Nuclear). The pharmaceutical activities of a "Unidad de Radiofarmacia" are authorised by the Ministry of Health of the concerned Autonomous Community (Consejería de Sanidad de la Communidad Autónoma).

3.5.3 Commercial Radiopharmacies

Spanish centralized radiopharmacies are authorised either as "radiopharmaceutical laboratory" or "radiopharmacy unit". They prepare single-dose RP from multi-dose vials and distribute them to neighbouring nuclear medicine centres. This is convenient especially for small hospitals and stand-alone nuclear medicine practices. They have only commercial interest: no research and development is carried out there *(adopted from: Peñuelas, talk, 2007)*. Radio-labeling of autologous cells may not be carried out by such commercial units.

3.5.4 Hospital Radiopharmacies

Spanish Hospital Radiopharmacies do the extemporaneous preparation of RP from generators, kits and precursors as well as blood-cell-labeling and compounding of RP for in-house use, which is done on the basis of "officinal and magistral preparation". As the authorisation process is decentralized and under the responsibility of local authorities, premises & equipment may differ among sites. A specialist in radiopharmacy is head of the unit *(adopted from: Peñuelas, talk, 2007)*.

3.5.5 Investigational RP for clinical trials

In order to produce a RP as IMP the place of manufacture must be authorised as Pharmaceutical Laboratory. A Hospital Radiopharmacy does not per se qualify for the manufacturing of IMP *(Peñuelas, talk, 2007).*This procedure is in line with the provisions on EU level.

3.6 Quality standards – GMP, GRPP and Ph.Eur.

As mentioned already, 70-80 % of the RP administered to patients are prepared extemporaneously from authorised generators, radionuclide precursors and kits. All RP that are not marketed, e.g. PET-radiopharmaceuticals for in-house use, are excluded form the scope of Directive 2001/83/EC as laid down in Article 2:

1. This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

Consequently, the rules for manufacturing of medicinal products, as laid down in Directive 2003/94/EC and explained in Eudralex Volume 4, are not mandatory for all those RP that are not intended to be placed on the market, are not produced involving an industrial process and are not intended for clinical trials.

This in-house preparation is commonly referred to as "compounding" to distinguish it from the (industrial scale) "manufacturing" of medicinal products. The different characteristics of industrial manufacturing and in-house compounding can be summarised as follows (Table 5):

Table 5: Comparison between Manufacturing and Compounding (modified from: *IAEA, 2004*)

	Manufacturing	**Compounding**
Producer	Manufacturer / Industry	(Hospital) radiopharmacy
Setting	Commercial	Clinical
Standard	Eudralex Volume 4 (EU GMP)	Varying Codes of Practice
Regulation	National medicinal regulatory authority	Professional bodies, institutions
Distribution	Public distribution	Practitioner->patient
Marketing	Yes	No
Permission	Marketing authorisation	Certain Exemptions

With regard to compounding "a major concern for individual patient preparations of pharmaceuticals in general is how quality requirements can be guaranteed when no marketing authorisation has been granted" *(Decristoforo, 2007).* Therefore, several initiatives try to establish suitable standards besides the EU-GMP-guidelines and in particular their Annexes I (sterile medicinal products) and III (radiopharmaceutical preparations).

In particular, the European Association for Nuclear Medicine (EANM) has published their views on how RP should be prepared: Good Radiopharmacy Practice, GRPP *(EANM, 2007)*. This guidance differentiates between kit-based and non-kit-based RP. Furthermore the European Pharmacopoeia contains a general chapter on compounding of RP which is

currently under review and a draft for consultation has been published in October 2011: European Pharmacopoeia: General chapter compounding of radiopharmaceuticals *(draft, open for consultation until 31st December 2011)*. The current Ph.Eur., version 7.3, contains 65 monographs of radiopharmaceutical preparations, underlining once more the importance and diversity of the field. GMP inspectors often refer the "PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments (PE-010-03)" as appropriate standard for hospital preparations.[7]

The common goal of all those initiatives is to safeguard the quality of RP at the moment of its administration to the patient. The standards have to bridge principles of radiological protection and of the manufacturing of medicinal products that are at some points contradictory.

When comparing the supra-national guidelines of PIC/S and EANM as well as the draft general chapter of the Ph.Eur. with the EU-GMP-guideline, namely Annex 3 Radiopharmaceuticals, it was noted that they all follow the same main principles. Only a few differences with high impact were identified:

1) One of the basic principles of GMP is the **strict separation of production and quality control.** This implies that enough personnel must be available to perform both tasks. Ph.Eur. and GRPP accept that this is not always possible in small centres. Both rooms and personnel have to serve several purposes. A compromise for small organisations is presented by German GMP inspectors. In the "Guidance for the supervision of PET-RP manufacturers" *(ZLG Aide mémoire Überwachung der Herstellung von PET-Radiopharmaka)* it is well taken into account that personnel working in a PET centre may switch between production and quality control "as long as the separation is assured on the basis of each batch".

2) PIC/S document contains special rules for extemporaneously prepared products in **emergency situations** with regard to documentation, quality of raw materials and sub-contracting. This is something that is not foreseen in the EU-GMP-guideline.

3) Another basic GMP principle is "to avoid cross contamination and mix-up of products". In case of compounding of RP, it is acceptable to use the **same room for multiple purposes** and products. Only autologuous patient's preparation shall be separated from other types of RP (GRPP and Ph.Eur.).

[7] It was observed during the preparation of this thesis, that the supervisory authorities of the member states have developed their own guidance documents on RP (e.g. ZLG, AFSSAPS, AEMPS). However, a detailed analysis of all would have been beyond the scope and time of the thesis.

4) According to GMP, the quality of raw materials needs to be established and controlled by means of incoming inspection. According to GRPP, checks of the certificate of analysis can be regarded as sufficient without full **vendor qualification**, which usually involves timely and costly audits.

5) To build suitable **facilities for the production of sterile medicinal products** has the biggest impact on the costs. For manufacturing of sterile RP, a Laminar flow unit (clean room class A) is acceptable inside a room of class C, if justified by documented risk assessment (PIC/S). Annex I EU-GMP-guideline requires class B as surrounding of A. Rooms of Class C and D may be in the same plant without further locks or change of clothes when going from one class to the other (PIC/S; GRPP). However, also Annex 3 of the EU-GMP-guideline offers some alleviation e.g. the possibility to produce sterile medicinal products in a class C environment as long as the process is performed in a closed system.

6) Essential for RP is the possibility to **release a product** before completion of all analytical tests (GRPP; Ph.Eur.). This applies to tests like sterility or radionuclidic purity that take long time or can only be carried out after decay of the radioactive isotope. According to PIC/S it is even not necessary to carry out microbiological control on every batch.

7) Of course, as the Ph.Eur. GRPP and PIC/S set standards for in-house manufacturing, guidance on **Contract Manufacture and Analysis**, **Complaints and Product Recalls** as well as **Self Inspection** are not given.

8) GRPP and Ph.Eur. are lacking clear **limits for environmental control** as are established in Annex I, EU-GMP-guideline, for particles and micro organisms in clean rooms. A proposal for suitable practice has been published recently by the French Society for Radiopharmacy (*Bruel, 2010*).

The attempt of a more detailed analysis of the differences is attached as Appendix C to this Thesis. In general, the standards for “compounding” and “manufacturing” do not seem to differ dramatically, considering that the EU-GMP-guideline leaves room for interpretation and adjustment to specific situations.

Apart from standards for manufacturing there are a lot more quality aspects related to RP under discussion, such as the question for acceptable quality of starting materials if they are not listed in the pharmacopoeia *(Verbruggen, 2008)*. However, a detailed investigation of such topics would have gone beyond the scope of this thesis.

4. Discussion

The discussion will try to answer the questions raised in the goals of the thesis based on the information presented in Chapter 3.

1) Which healthcare establishments are authorised for extemporaneous preparation of RP in the different Member States? What is their legal basis?

As demonstrated in Chapter 3, the Member States except for Germany have developed different concepts of Radiopharmacy Units, Unidad de Radiofarmacia, PUI etc. inside their national health care system. The word "radiopharmacy" used for those institutions implies that they are a pharmacy or have a "pharmacy-like" status in most countries. Therefore, they can profit from the rules for officinal and magistral preparation. Besides the pharmacy status there are other establishments that may prepare RP without the need for a marketing authorisation (Table 6).

Table 6: Establishments authorised for extemporaneous preparation without need for MA

	DE	**UK**	**FR**	**ES**
(Hospital) Pharmacy	Yes (AMRadV)	Yes (Section 10)	Yes (PUI)	Yes (Unidad de Radiofarmacia)
Clinical institution	Yes (AMRadV) for diagnostic purposes only	No	No	No
Physician	Yes (§ 13 (2b) AMG)	Yes (Medicines for Human Use (Marketing Authorisations etc.) Regulations 1994)	No	No
Other (commercial) organisations	No	Yes (Specials' License)	No	Yes (Unidad de Radiofarmacia)

According to the transformation of Article 7 of Directive 2001/83/EC into AMRadV hospital pharmacies are the authorised health care establishments for extemporaneous preparations of RP. Germany has about 400 hospital pharmacies however it is presumed that only few are involved in the supply of RP. Therefore in Germany the most extemporaneous preparations are made based on the exemption for clinical institutions (AMRadV), applicable to products used for diagnosis or based on the provisions of § 13 (2b), "manufacturing under the responsibility of a physician". A possibility for third party supply, e.g. by commercially operating organisations is not foreseen in Germany. The product prepared by such an

organisation even though originating from authorised kits, generators and precursors would require a MA. Both the Specials' License concept in UK and the Unidad de Radiofarmacia in ES allow for the distribution of such pre-assembled products to others. Commercially operating organisations such as private companies may be licensees in UK. PUI in France may deliver to others but as they are part of the national health system they cannot be compared to the others. The preparation under the responsibility of a physician without pharmacy involved is the most widely used regulatory pathway in Germany. This would be inconceivable in France *(Hallouard, 2011)*.
Notably Spain exempts not only extemporaneous preparation from authorised kits, generators and precursors but also PET radiopharmaceuticals in general from the requirement of MA if certain conditions are met. Germany has a similar approach with the AMRadV, however limiting not to PET products put to products for diagnostic use.

2) Which quality standards are applicable to the manufacture of different types of radiopharmaceuticals? What are the main differences to conventional "full GMP" according to Directive 2003/94/EC and the EU-GMP-guideline?

The demarcation line whether "full" GMP applies or not seems to be very clear: The legislation throughout EU distinguishes between medicinal products manufactured to be placed on the market, using industrial techniques and the in-house preparation in (academic) hospitals or pharmacies for specific patients. On the first glance, this seems to be an appropriate approach with clear criteria to distinguish which product falls in which group. "In many cases, radiopharmaceuticals are prepared in a daily routine for in-house use or in some cases also for neighbouring hospitals (satellite concept). Characteristically, individual doses for a few patients based on individual prescriptions are prepared to be used within the same working day. This is in contrast with industrial manufacturing where batches for a great number of patients are produced." *(Note on the Ph.Eur. General Chapter 5.19 – Draft).* However, in the case of RP small-scale preparations are carried out "in both industrial sites (GMP licensed facilities) and non-industrial sites (hospital pharmacies, nuclear medicine departments, PET centres)" *(Verbruggen, 2008)*. These "industrial sites" are often small enterprises that deliver their product to third parties ("placing on the market") but the output of their production process is not "industrial" when compared to conventional medicinal products. Furthermore, the production processes applied by the commercially operating centres do not differ from those used for in-house compounding. It seems to be adequate to create a category of "semi-industrial" manufacturing for those smaller enterprises. A suitable standard for preparation both for non-commercial and semi-industrial manufacturers could be the EANM "Good Radiopharmacy Practice" in conjunction with the general chapter of the

Ph.Eur.. As shown in Chapter 3.6 there are only a few differences to "full" GMP. However, these are points that have a strong impact on the budget of an enterprise: the size and type of clean room facilities and equipment, sufficient personnel to ensure both production and quality control and the need for a QP.

An overview about the applicability of "full" GMP or other standards on the extemporaneous preparation in the establishments authorised according to national law is given in Table 7. In France and Spain, authorities made provisions for the standards that are applicable for the extemporaneous preparation *(AFSSAPS: bonnes pratiques de préparation and ES: Annex II of RD 479/1993 as well as Normas de Buena Preparación Radiofarmacéutica)*. In Germany there are currently no provisions for the preparation under § 13 (2b) except for the pharmacopoeial standards *(EFG Votum V12001, 2009)*. In contrast, for clinical institutions operating under AMRadV, full GMP applies as they need a manufacturing license according to § 13 AMG. In general the same type of products in comparable quantity is manufactured under both provisions. This discrepancy in quality standards is difficult to understand and seems not to be adequate. The situation for hospital pharmacies in Germany is not clear. According to § 13 (2) AMG they would need a manufacturing license for RP subjecting them under GMP. However, the AMRadV – as *lex specialis* – exempts the products from the requirement of MA but does not specify on the need for manufacturing license.

Table 7: Applicability of GMP or other standards to the extemporaneous preparation

	DE	**UK**	**FR**	**ES**
"Full" GMP	AMRadV: clinical institution with manufacturing license;	Units with Specials' license	-	-
GMP for extemporaneous preparation	-	Units under Section 10	PUI	Unidad de Radiofarmacia
No official standard	§ 13 (2b) Hospital pharmacy (?)		-	-

Table 7 shows the variability of standards for the extemporaneous preparation in the four countries. Some authors compare RP with advanced therapy medicinal products (ATMP) where by means of Regulation EC No. 1394/2007 it was introduced that "even for the industrial manufacturing […] GMPs should be adapted to reflect the specific nature of such products and of their manufacturing process" *(Decristoforo, 2009).* A common, harmonised standard for small-scale preparations both in public and private institutions should be considered.

3) Which personnel is involved in manufacturing and release of RP, what kind of education and qualification is required according to the law of the respective Member State?

A product manufactured industrially and with a marketing authorisation, needs to be released by a Qualified Person. This is the case for all Member States; however, the educational requirements for QPs releasing RP vary. In France and Spain, Radiopharmacy is a speciality for pharmacists required to take over a responsible role in the manufacturing of RP. In UK post-graduate courses in Radiopharmacy are available but not mandatory for QPs. In DE there is no formal (radio)pharmaceutical university education, but 3 years of relevant experience. Pharmacists, chemists, biologists or physicians may be appointed QP.
With regard to the extemporaneous preparations the requirements for responsible persons are as variable the legal bases of the preparations: FR and ES require a Radiopharmacy Specialist in the Radiopharmacy Units to release the products. In UK, depending on the legal basis of the unit there is either a pharmacist involved (section 10) or the quality control manager is responsible for release (specials' license unit). DE: whenever a unit has a manufacturing license (AMRadV) then a QP must be available while products produced under § 13 (2b) AMG are under the responsibility of the physician.

4) How is the situation regarding innovation and clinical development of new radiopharmaceuticals? Can hindrances by certain legal regulations be identified?

"Over the last 10 years, many products have been discontinued from the UK market due to reasons ranging from being commercially non-viable to non-availability of suitable grade of active pharmaceuticals ingredients. Many of these products have either no licensed equivalents or were the sole products on the market for the certain indications. The range of procedures that Nuclear Medicine departments can now offer has been sharply reduced." *(UK Radiopharmacy Group, 2009).* In addition to discontinued products, newly granted MA are rarely reported. Some RP are not suited for commercialisation and therefore no company will ever apply for MA *(Decristoforo, 2005)*. However, there is room for improvement.

Marketing authorisation for PET diagnostics

During the last decade PET has evolved as diagnostic technique and its use in clinical routine is still growing further. However, when looking for MA granted in Germany there are only a few authorised products with ^{18}F-labelled substances for PET: Fludeoxyglucose (^{18}F), Fluormethylcholine (^{18}F), Sodium Fluoride (^{18}F) and F-DOPA (^{18}F). For other PET-isotopes like C-11 or Ga-68 there are no MA existing. Some of the substances are monographed in

the Ph.Eur.. Those substances have been developed by research institutions over the years and today a number of substances are used daily in clinical routine on the basis of exemptions, such as AMRadV (DE) or the PET-RP according to Article 47 RD 1345/2007 (ES) or the Specials' License (UK) as well as magistral preparations.

It is clear that marketing authorisations would simplify the regulatory picture and improve the supply situation. However, as the market share is small and numerous manufacturing sites are necessary to cover the European market, return on investment of a full clinical development program is insecure. Furthermore, most of the active substances that are used are not patented or not patentable. This, of course, makes it unattractive for a pharmaceutical company, in particular when it comes to extremely short-lived RP *(Decristoforo, 2005)*.

The situation today with those PET-compounds, is to some extent comparable to the situation in the late 1980 when RP were first subjected under pharmaceutical legislation. Some of the compounds already present the standard of care for certain indications even though they are used on a non-licensed or off-label basis.[8] In addition, this non-licensed or off-label use is limited to hospitals and most of the private nuclear medicine practices do not have access to such medicinal products as long as they lack a MA. A solution might be a coordinated procedure as the one following Directive 89/343/EC offering an abridged MA procedure for certain PET compounds.

A similar encouraging attempt has been undertaken by Swissmedic already in 2010: the Swiss authority published a proposal for a simplified MA procedure including a list of RP that are eligible for MA based on "well-established use" *(Positiv Liste: Radiopharmazeutika mit well-established use Status, www.swissmedic.ch*). A similar approach in the EU could help to improve the supply situation for most products and the legal situation for supervisory authorities, companies and physicians involved *(Ehlers, 2010)*.

Clinical trials

As described in Chapter 3.1, the clinical trials directive *(Directive 2001/20/EC)* does not contain any exemptions similar to the concept of the extemporaneous preparation for authorised products. However, due to the special nature of RP, especially with short-lived isotopes, the final product to be administered cannot be analysed completely before use. The quality of the starting materials is essential to assure the quality of the finished product,

[8] Reference is made to the public assessment report of the Art. 45 procedure for Octreoscan (^{111}In-Pentetreotide), FR/W/007/pdWS/001, where the rapporteur concludes that under certain circumstances "it can be discussed whether it is preferable to use pentetreotide (^{111}In) which is registered in adults or an octreotide derivate labeled with ^{68}Ga for PET which gives better images for a lower irradiation but is prepared for the moment as an officinal product".

especially “when the final preparation is released without further purification” *(Verbruggen, 2008)*. As a consequence, an IMP could be composed of a GMP-produced kit and a GMP-produced radionuclide precursor for radio-labeling at the site of administration. Following a strict interpretation of Directive 2001/20/EC, each clinical trial site needs a manufacturing license for each IMP to be used. This has a big impact on finance and time-lines in clinical development especially for multi-centre trials. Germany has a very strict few on the topic by requesting manufacturing licenses from the trial site *(Meller, 2012)* whereas other Member States accept that the clinical trial sites do a “compounding” in accordance with procedures described in the IMPD. In France, the PUI are empowered by law to do “preparations required for clinical trials”. In Germany, only the “reconstitution” of a medicinal product at a trial site is feasible without a manufacturing license.

A compounding concept might not be adequate for PET-RP that involves complex synthesis of the active substance followed by purification steps in its manufacturing (F-18, C-11 etc.). However, the availability of PET-isotopes such as Ga-68 or Zr-89 would allow for the development of a kit-chemistry with starting materials of well-controlled quality. Therefore, an approach on European level to establish a similar regulation as the Article 7 of Directive 2001/83/EC for clinical trials would be a valuable contribution to promote clinical development and innovation.

5) Are there concepts / achievements in other countries that should be adopted to improve the German system? What prerequisites or legal changes would be necessary?

The survey of applicable laws has revealed some small deviations of the German law from the EU level. Furthermore, solutions on specific topics from other Member States might help to improve the situation in Germany.

Formal deviations

It was observed that the definitions for RP according to the AMG are not an exact transformation of the definitions given in Directive 2001/83/EC, as amended. A definition of “kit” is missing in the German law while the definition of “radioactive medicinal product” (§ 4 (8)) includes not only ready-to-use RP but also precursors and radionuclide generators. The national laws of FR, ES and UK are clearer in this respect, stating that “kits, precursors and generators” need MA when they are prepared industrially but not summarising them under the term “medicinal product”. The German definitions should be aligned with EU provisions.

Furthermore, it was noted that the labelling requirements of the primary packaging (vial) according to AMG and AMRadV are more extensive than they necessarily needed to be according to Art. 66 of Directive 2001/83/EC. This might seem a minor issue of low importance. However, in practice it causes problems for the manufacturers as the space on the vials is limited. And it remains questionable who will profit from all the details written in small letters on the vial. The personnel in a nuclear medicine department will rather consult the label on the lead shield or other accompanying documentation due to radiation protection reasons. Therefore, minimum information that allows for identification of the product should suffice on the vial. Furthermore, if less information had to be placed on the label, a bigger typesize could be chosen allowing for readability from longer distances or behind lead glass windows. A change in labelling requirements for the primary packaging of RP should be considered aligning the German provisions with the EU level.

Supply situation following 15th amendment

The situation in Germany is characterized by a large number of free nuclear medicine specialists practising outside hospitals. Following the 15th amendment of the AMG the supply situation with RP was impaired for them due to the deletion of § 4a (3) *(DGN, 2009).* Due to the lack of commercially available products with MA for PET, the only way for those physicians is to do the manufacture under § 13 (2b) AMG. As a consequence educated personnel and suitable rooms must be available, especially for novel (PET-)products, requiring a more sophisticated production technique than conventional SPECT-kits.

A commercially operating centralised radiopharmacy unit could improve the situation not only for innovative but also for conventional products prepared extemporaneously. From a quality and organisational point of view, such a centralised unit would have a number of advantages: A specialised unit would be efficient, economical in the purchase of kits or radionuclides, reaching a consistent (high) quality of products and requiring a smaller number of specialised staff *(ARSAC, 2010)*. Even the supervision of a small number of centres by the competent authorities could be organised more efficiently.

It has to be admitted that not all products would be suited for a centralised preparation due to a too fast decay of the respective isotopes. However, with regard to future technical development and more sophisticated manufacturing techniques the preparation of RP under § 13 (2b) AMG without obligatory quality standards does not seem appropriate. Especially, when considering that almost 2 % of the population receive a RP each year. A centralised radiopharmacy unit under adequate supervision would be a step ahead.

Despite all advantages, such a preparation of individual doses by a commercial unit for third parties is not foreseen in the law. Legally, it would only be possible if the centralised radiopharmacy unit worked under a marketing authorisation for the compounded product,

although it was prepared from authorised kits, precursors and generators and upon medical prescription.

There are other types of medicinal products, where “post-release manipulations” are required to meet special patients’ needs. A similar case for example is the preparation of cytostatic drugs or parenteral nutrition for individual patients. Pharmacies are allowed to do these preparations by using authorised ingredients and upon medical prescription (§ 13 (2) AMG and § 11 (2) APOG) which would in principle work for RP as well (§ 2 AMRadV). However, as the pharmacies in Germany are traditionally not involved in the preparation of RP solutions must be found outside this regulatory path.

One option would be to clarify or extend the scope of § 13 (2b) AMG in such a way that physicians may authorise persons in specialised laboratories to manufacture (non-)authorised RP under their responsibility and according to their prescriptions. First attempts of establishing this practice were judged differently by the supervisory authorities of the Federal States: few allowed this practice under special circumstances (namely, manufacturing license granted and a contract closed between physician and manufacturer) while others were clearly opposed to it. The most important question was whether the responsible physician had to be personally present at the site of manufacturing or during the manufacturing or not.

Another option to introduce “radiopharmacies” in Germany would be to change the provisions of AMRadV and open it for commercial suppliers. According to § 2 AMRadV, clinical institutions may prepare diagnostic RP on the basis of a manufacturing license and for not more than 20 patients per week. In addition hospital pharmacies may prepare RP form authorised kits, precursors and generators. By a small change the scope of the AMRadV could be extended to commercial suppliers well under the control of pharmaceutical supervisory authorities and following the GMP guidelines for preparations upon medical prescription.

A third option would be the adoption of the concept of “Specials’ License” from UK not necessarily limited to RP. Rules for importing medicinal products that are authorised elsewhere are contained in the German Medicinal Products Act (§ 73) while provisions for manufacturing outside the pharmacy track are not given. However, such a change, if not restricted to RP, may lead to situations similar to Spain in the 1990ies when the concept of radiopharmacy units was introduced *(Marcos Moreno, 2003).* Pharmacists were appealing to court as the found their privileges of preparing and dispensing medicinal products were violated.

Therefore, a change in AMRadV enabling both the extemporaneous preparation from authorised kits, precursors and generators and the preparation of certain non-authorised but state-of-the-art PET-products would be the most easy way to achieve.

6. Conclusion

"Radiopharmaceuticals are among the most highly regulated of materials administered to patients because they are controlled both as medicinal products and as radioactive substances" *(UK Radiopharmacy Group, 2012)*. In addition, their peculiarities have resulted in a number of special provisions in the pharmaceutical legislation on EU level that have been transformed differently into the Member States laws. This heterogeneous situation is connected to the different organisation of the healthcare sector in the respective Member State and to the degree of involvement of pharmacists in the preparation of RP. A complete harmonisation of all differences would have too severe effects on the traditionally grown structures and a success is rather insecure.

However, some adjustments on European level would be worth considering. All Member States have developed special provisions to enable the use of RP for PET diagnosis. These products represent the standard of care in some indications. However, it is rather improbable that they will be brought to a MA based on a full clinical development program. A solution could be a coordinated procedure similar to that initially subjecting RP to the pharmaceutical law in the early 1990ies. To facilitate clinical developments a compounding concept comparable to the Article 7 of Directive 2001/83/EC could be introduced. Clinical trial medication could be prepared at the site of administration based on GMP-produced IMP-kits, IMP-precursors or IMP-generators without the formal need for a manufacturing licensed for the ready-to-use product at each trial site.

Quality standards for the preparations are varying particularly and with regard to inspection practice a EU harmonisation would be fruitful. One characteristic of the commercialisation of RP is the need for several decentralised manufacturing sites to cover a certain territory. Even though run for commercial purposes they do not work on the same scale as big pharmaceutical plants for conventional medicinal products. However, they have to follow the same GMP rules. Those RP-production facilities could be regarded as "semi-industrial" and adherence to a tailored GMP-approach such as GRPP could be manifested by adequate means in the European law.

Particularly complex, though explained by historic development, is the situation in Germany. A variety of legal bases results in extreme differences in the quality standards applicable on the manufacturing of what is basically the same product. Furthermore, the supply situation for free nuclear medicine practices is difficult as their access to unlicensed products is limited in comparison to physicians in hospitals. Commercial organisations ("radiopharmacies") could help to improve the situation if they were authorised for extemporaneous preparations and manufacturing of unlicensed product by means of AMRadV or a concept similar to the Specials' License that is available in UK. By applying common standards on those preparations their quality would be ensured and improved.

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www.snrph.org (Syndicat national des radiopharmaciens)

www.ukrg.org.uk (UK radiopharmacy group)

www.nuklearmedizin.de (Deutsche Gesellschaft für Nuklearmedizin)

www.legifrance.gouv.fr (French legislation)

http://noticias.judicias.com (Spanish legislation)

www.legislation.gov.uk (UK legislation)

www.mhra.gov.uk (UK health authority)

www.radiofarmacia.org (Spanish Radiopharmacy Society)

Appendix A: (Inter)national organisations cited in the text

To improve readability of this thesis, a short description of European and national organisations acting in the field of radiopharmaceuticals is given here. Most of the information has been taken from the society's websites (January – April 2012).

AGRR: Arbeitsgemeinschaft Radiochemie/Radiopharmazie

The working group Radiochemistry/Radiopharmacy (AGRR) has been founded in 1992 under the umbrella of the Deutsche Gesellschaft für Nuklearmedizin (DGN). It unites radiochemists, biological scientists, radiopharmacists and experts of neighboring sciences, who work on the field of radiopharmaceutical chemistry and radiopharmacy as researcher or manufacturer. Most of its members are located in Germany, Austria and Switzerland. Many representatives from industry are among ist members (producers of radiopharmaceuticals, and of equipment). The AGRR offers a platform for exchange of experiences and collaboration in joint projects and support in the post-graduate education. For the harmonisation of the education, a programm was develloped that offers the possibility for chemists, pharmacists and biologists to qualify for the manufacturing of radiopharmaceuticals in the EU. (http://www.hzdr.de/FWB/dgn/)

ARSAC: Administration of Radioactive Substances Advisory Commitee

Regulation 2 of the Medicines (Administration of Radioactive Substances) Regulations 1978 (MARS Regulations 1978) requires that any doctor or dentist who wishes to administer radioactive medicinal products to humans should hold a certificate issued by Health Ministers. The Regulations also established a committee to advise Ministers on applications. The Administration of Radioactive Substances Advisory Committee (ARSAC) was set up to: advise Health Ministers with respect to the grant, renewal, suspension, revocation and variation of certificates and generally in connection with the system of prior authorisation required by Article 5(a) of Council Directive 76/579/Euratom. The majority of committee members are medical doctors and are appointed by Ministers from within the UK as independent experts in their own field such as nuclear medicine. The Committee normally meets twice a year. (www.arsac.org.uk)

DGN: Deutsche Gesellschaft für Nuklearmedizin

The Deutsche Gesellschaft für Nuklearmedizin e.V. (German Society for Nuclear Medicine) is a scientific society with the goal to promote nuclear medicine in basic and applied research in the field of diagnosis, therapy and radiation protection. This happens on national and more and more international level through education and promoting of young researchers, quality assurance, norming activities, public relations as well as annual meetings. Scientific organ is the journal "Nuklearmedizin". The society has currently 1550 members among them physicians specialised in nuclear medicine as well as other medical disciplines, scientists and engineers. The DGN is located in Hannover. (www.nuklearmedizin.de)

EANM: European Association for Nuclear Medicine

The European Association of Nuclear Medicine (EANM) is the umbrella organisation of nuclear medicine in Europe and represents the sector towards the European Institutions. Within this role, the EANM aims at advancing science and education in nuclear medicine for the benefit of public health as well as at promoting and co-ordinating, throughout Europe and beyond, discussion and exchange of ideas and results relating to the diagnosis, treatment, research and prevention of diseases through the use of unsealed radioactive substances and the properties of stable nuclides in medicine. The goal of the EANM is thus to provide a suitable medium for the dissemination and discussion of the latest results in the field of

nuclear medicine and related subjects. In 1985, the EANM was founded by merging the Society for Nuclear Medicine Europe and the European Nuclear Medicine Society. Over recent years, the total EANM membership has risen to over 3,000 individual members who are physicians, scientists, technologists or other persons working in nuclear medicine or related fields. Furthermore, the number of EANM National Societies (member states of the Council of Europe) currently amounts to 35. Thus, today, the EANM is the largest organisation dedicated to nuclear medicine in Europe. In this role, it has become the umbrella organisation which represents the whole sector towards the European (Politcal) Institutions. (www.eanm.eu)

EURATOM: European Atomic Energy Community

Together with the EEC Treaty the Euratom Treaty was signed in Rome in March 1957 and entered into force on 1 January 1958 (“Treaties of Rome”). The aim of creating a European Atomic Energy Community (Euratom) was to tackle the general shortage of "conventional" energy in the 1950s. The six founding States (Belgium, France, Germany, Italy, Luxembourg and the Netherlands) looked to nuclear energy as a means of achieving energy independence. The general objective of the Treaty is to contribute to the formation and development of Europe's nuclear industries, so that all the Member States can benefit from the development of atomic energy, and to ensure security of supply. At the same time, the Treaty guarantees high safety standards for the public and prevents nuclear materials intended principally for civilian use from being diverted to military use. It is important to note that Euratom's powers are limited to peaceful civil uses of nuclear energy. The Euratom Treaty introduces an extremely strict and comprehensive system of safeguards. The European Commission is empowered to send inspectors to the Member States and, in case infringement, to impose sanctions on the persons responsible. The Euratom safeguards are applied in conjunction with those of the International Atomic Energy Agency (IAEA) under tripartite agreements concluded between the Member States, the Community and the IAEA.
In addition to the institutional triangle (Council, Commission and European Parliament) and the Courts (Court of Justice and Court of Auditors), two specific Euratom bodies are acting to fulfil the tasks entrusted to the Community: the Supply Agency and the Safeguards Office. Unlike the EC Treaty, no major changes have ever been made to the Euratom Treaty, which remains in force. The European Atomic Energy Community has not merged with the European Union and therefore retains a separate legal personality, while sharing the same institutions.
(http://europa.eu/legislation_summaries/institutional_affairs/treaties/treaties_euratom_en.htm)

IAEA: International Atomic Energy Agency

The IAEA was created in 1957 in response to the deep fears and expectations resulting from the discovery of nuclear energy. US President Eisenhower's Atoms for Peace address to the General Assembly of the United Nations in 1953 lead to the IAEA Statute, which was approved by 81 nations in 1956. The Statute outlines the three pillars of the Agency's work - nuclear verification and security, safety and technology transfer." Today, the IAEA Secretariat is made up of a team of 2300 multi-disciplinary professional and support staff from more than 100 countries. The Agency’s headquarter is located in Vienna, Austria and offices are run in Toronto, Tokyo, New York and Geneva. Research laboratories are located in Seibersdorf, Austria, and in Monaco. Six major IAEA departments - management, nuclear sciences and applications, nuclear energy, nuclear safety and security, technical cooperation, and safeguards and verification - set the organizational framework. IAEA programmes and budgets are set through the decisions of its policymaking bodies - the 35-member Board of Governors and the General Conference of all Member States. The IAEA has 151 Member States, as of November 2010. Eighteen ratifications were required to bring the IAEA's Statute into force. (www.iaea.org)

ICRP: International Commission on Radiological Protection

The aim of the International Commission on Radiological Protection (ICRP) is to prevent cancer and other diseases and effects associated with exposure to ionising radiation, and to protect the environment. ICRP is an independent, international organisation with more than two hundred volunteer members from approximately thirty countries across six continents. These members represent the leading scientists and policy makers in the field of radiological protection. ICRP is funded through a number of ongoing contributions from organisations with an interest in radiological protection. Since 1928, ICRP has developed, maintained, and elaborated the International System of Radiological Protection used world-wide as the common basis for radiological protection standards, legislation, guidelines, programmes, and practice. ICRP has published more than one hundred reports on all aspects of radiological protection. The International System of Radiological Protection has been developed by ICRP based on (i) the current understanding of the science of radiation exposures and effects and (ii) value judgements. These value judgements take into account societal expectations, ethics, and experience gained in application of the system. (www.icrp.org)

SERFA: Sociedad Española de Radiofarmacia

The spanish society for radiopharmacy was founded in 1989 by a group of radiopharmacy professionals with the aim of promoting radiopharmay in spain and as a reaction to the transformation of the legislation in the European Union with regard to radiopharmaceuticals. The SERFA was engaged in establishing a post graduate training in radiopharmacy and ist still engaged in formation and scientific progress of its membership.
(www.radiopharmacia.org)

SNRPH: Syndicat Nationale des Radiopharmaciens

The French National Union of Radiopharmacists has been founded in January 2000.
Uniting in general radiopharmacists of all different backgrounds and exercising radiopharmacy, it has the following goals:

- To promote the studies of radiopharmacy, to investigate the quality and excellence in all fields of this discipline and to develop the role of the radiopharmacists in the health care establishments.
- To defend professional, financial and ethical interests of its supporters.
- To study the problems that arise in connection with the education, qualification, recruitment and status of its members.
- To inform and contribute to the education of its supporters.
- To favour professional relationships and to assure the coordination between its members and with other health care professionals
- To represent its members at competent authorities (www.snrph.org)

SoFRa: Société Française de Radiopharmacie

The French Society for Radiopharmacy unfortunately has no website and no further information could be obtained.

UK radiopharmacy group

The origins of the UK Radiopharmacy Group date from 1976 and were an initiative by a small group of practising Radiopharmacists to work together for the advancement of Radiopharmacy. The inaugural meeting was held 1977, a set of proposals was formulated and as a result the Regional Radiopharmacists subcommittee was formed and steadily extended to include representatives of Regional Health Authorities, plus individuals from academia and the Medicines Control Agency. One of the first tasks of the Group was to examine the required facilities for the hospital preparation of radiopharmaceuticals. In 1980

these examinations of quality assurance procedures led to the publication entitled "Quality Assurance of Radiopharmaceuticals - a Guide to Hospital Practice". During these early years the Radiopharmacy subcommittee was the first non-clinical specialist group in the British Nuclear Medicine Society who provided enormous support. As a result of a regional reorganisation of the NHS, the subcommittee considered is future as a stand-alone advisory group on Radiopharmacy the UK Radiopharmacy group came into being in 1995.
Today the Group consists of a minimum of eight public sector employees with active responsibility for Radiopharmacy services. Representatives of the MHRA, ARSAC, The National Quality Assurance Committee, IPEM, Academia and researchers in the field will also be invited. Goals of the Group are authoritative leadership in the field of radiopharmacy, promote further developments and give guidance on quality related aspects. Meeting minutes are distributed to MHRA and several NHS committees in Great Britain.
(http://www.bnms.org.uk/general/ukrg-homepage.html)

WNA: World Nuclear Association

The World Nuclear Association is the international organization that promotes nuclear energy and supports the many companies that comprise the global nuclear industry. WNA arose on the foundations of the Uranium Institute (UI), established in London in 1975 as a forum on the market for nuclear fuel. In 2001 the UI mandated itself to build a wider membership and a greater diversity of activities. The goal was to develop a truly global organization geared to perform a full range of international roles to support the nuclear industry.
Since WNA's creation in 2001 membership has expanded three-fold to encompass virtually all world uranium mining companies, reactor vendors and major nuclear engineering as well as waste management companies. Other WNA members provide international services in nuclear transport, law, insurance, brokerage, industry analysis and finance.
Today WNA serves its membership, and the world nuclear industry as a whole, through actions to: sharing knowledge and insight on developments, strengthen the operational capabilities, speak authoritatively for the nuclear industry in key international forums and improve the international policy and public environment.
An overarching WNA purpose is to foster interaction among top industry leaders to help shape the future of nuclear power. Led by senior industry executives, the WNA Board sets priorities, budgets and fees to support a diversity of WNA activities, including more than a dozen industry Working Groups, which are staffed by a small London-based secretariat. All WNA activities focus on objectives outside the scope of national associations, intergovernmental organizations and the industry's reactor safety organization. WNA represent the industry in international forums, such as IAEA and NEA advisory committees (transport and nuclear safety), United Nations policy forums (sustainable development) and ICRP (radiological protection). (http://world-nuclear.org)

Appendix B: Examples for Radiopharmaceuticals

Examples for different types and classes of products fulfilling the definition "radiopharmaceuticals" (non-exhaustive list adopted from *Schirbel 2006*, and completed by consulting: AMIS-Datenbank; www.ema.europa.eu; www.hma.eu/mri; Ph.Eur. 7nd edition).

Active Substance	**Pharmaceutical form**	**Indication**	**Type of radiation/ Half-life**	**marketing authorisation and/or Ph.Eur. monograph**
Yttrium (^{90}Y) chloride	Radiopharma-ceutical pre-cursor, solution	Radiolabeling of molecules	β / 64,1 h	CP
(^{90}Y)-Zevalin	Kit for the preparation of a solution for injection	Treatment of lymphoma (radioimmuno-therapy)	β / 64,1 h	CP
(^{90}Y)-Onalta	Solution for injection	Treatment of neuroendocrine tumors	β / 64,1 h	Clinical trials, non-licensed use
(^{177}Lu)-Lutate	Solution for injection	Treatment of neuroendocrine tumors	β / 64,1 h	Clinical trials, non-licensed use
Sodium Fluoride (^{18}F)	Solution for injection	Diagnosis of bone metastase (PET)	β+ / 107 min	National, MRP Ph.Eur.
Fludeoxyglucose (^{18}F)	Solution for injection	Diagnosis in oncology, neurology, inflammatory diseases (PET)	β+ / 107 min	National, MRP, Ph.Eur.
Fluormethylcholine (^{18}F)	Solution for injection	Diagnosis of bone metastases of prostate cancer (PET)	β+ / 107 min	MRP
^{18}F-DOPA	Concentrate for the preparation of a solution for injection; solution for injection	Diagnosis of M. Parkinson etc. (PET)	β+ / 107 min	MRP, Ph.Eur.
^{99}Mo/^{99m}Tc	Radionuclide generator	Thyroid-Imaging, Radiolabelling of tracers for targeting several organs	γ / 6 h	National, MRP
^{82}Sr/^{82}Rb	Radionuclide generator	Myocardial perfusion imaging (PET)	β+ / 75 sec	EU: Clinical trials; US: authorised

$^{68}Ge/^{68}Ga$	Radionuclide generator	Radiolabelling of molecules (PET)	β+ / 67 min	EU: clinical trials; magistral preparations; unlicensed use;
(^{99m}Tc-) Hexamethyl-propylenaminoxim	Kit for the preparation of a solution for injection	Brain perfusion (SPECT)	γ / 6 h	National, MRP
(^{99m}Tc-) Ethylcysteinat-dimer	Kit for the preparation of a solution for injection	Brain perfusion (SPECT)	γ / 6 h	National, MRP
^{99m}Tc-Tetrofosmin	Kit for the preparation of a solution for injection	Myocard perfusion (SPECT	γ / 6 h	National; MRP
^{99m}Tc-MIBI	Kit for the preparation of a solution for injection	Myocard perfusion (SPECT	γ / 6 h	National, MRP
(^{99m}Tc) Mercaptoacetyl-triglycerin (MAG3)	Kit for the preparation of a solution for injection	Kidney function (SPECT	γ / 6 h	National, MRP
^{99m}Tc-labeled colloidal Human Serum Albumin	Colloidal suspension	Lung ventilation	γ / 6 h	National, MRP
^{111}In-oxinate	Solution	Labelling of blood cells	γ / 6 h	National, MRP
(^{111}In)-OctreoScan	Kit for the preparation of a solution for injection	Diagnosis of pancreatic neuroendocrine tumors (SPECT)	γ / 6 h	National, MRP
^{11}C-raclopride	Solution for injection	Diagnosis of M. Parkinson, D2-Receptor-occupancy (PET)	β+ / 20 min	Ph.Eur. In-house
(^{81m}Kr) Krypton	Inhalation gas	Lung	γ / 13 sec	Ph.Eur.
Sodium Iodide (^{131}I)	Capsule	Therapy of hyperthyroidism, M. Basedow etc.	β / 8,1 d	National, MRP

Appendix C: Comparison of quality guidelines

EU-GMP-guideline and guidelines for (hospital) small-scale preparation and compounding

The following table summarises the attempt of comparing the EU-GMP-guideline applicable to industrial manufacturing of medicinal products with the proposals for small-scale preparation of (radio)pharmaceuticals for in-house use. In order to reduce complexity of the table, only those aspects of the EU-GMP-guideline are mentioned, where at least one difference in another guidance document could be identified.

Topic	**EU GMP guideline** **Incl. Annex 1 and Annex 3**	**cGRPP** Part A: Kit-based RP Part B: PET-RP	**PIC/S PE 010-03 Manufacture […] in healthcare establishments incl. Annex 1 sterile preparations**	**Ph.Eur. General Text on compounding of RP - Draft**
Scope	industrially manufactured medicinal products; Annexes with guidance for special products such as sterile, semi-solid, herbals or radiopharmaceuticals	Detailed and practice oriented guidance for small-scale preparations of PET, therapeutic or other radiopharmaceuticals which are not intended for commercial purposes or distribution	Whereas PIC/S Guide PE 009 applies to industrial manufacture of distributed medicinal products, the basic requirements presented in this Guide apply to the preparation of medicinal products normally performed by healthcare establishments for direct supply to patients. […] National legislation and regulatory policies laid down by the relevant competent authority should always be referred to when determining the extent to which the provisions laid down in this document are binding.	Radiopharmaceutical compounding and preparations in radiopharmacies including kit-based preparations, preparations made on-site (PET or others with short-lived radionuclides) Cross-reference to PIC/S PE 010-03 and cGRPP
Quality Management	Chapter 1	Chapter 2: Quality assurance There has to be a quality assurance unit that can oversee preparation operations to ensure that a radiopharmaceutical of sufficient quality is prepared. Part B: Quality assurance unit: examine, approve or reject components, containers, closures, materials, packaging materials labelling and finished product,	1. Quality assurance system Quality assurance represents the sum of organised arrangements made with the object of ensuring that medicinal products are of the quality required for their intended purpose. - designed according to the latest state of knowledge - production and control operations clearly specified	

		approve or reject specifications, review preparation records *(tasks of quality control unit or QP)*	- correctly processed, checked and stored in accordance with the defined procedures and released by a competent person - measures in place to assure the quality throughout the shelf-life - documentation systems in place and maintained	
Personnel	Chapter 2 Basic principle: "Strict separation of production and quality control"	"in small facilities the responsibility for production and quality control may rest with the Responsible Person"	Establishment and maintenance of quality relies upon personnel - Responsible Person responsible for quality and compliance with this guideline - Adequate number of competent personnel - Competency level depending on duties and requirements of the activities undertaken by the organisation - Organisation chart showing the organisation structure - Duties and responsibilities layed down in job descriptions Training and continued education; Hygienic behaviour and appropriate clothing	
Premise and Equipment	Chapter 3 Basic principle: "avoid cross contamination"	Part B In small PET centres the same room can be used for multiple purposes. For example the preparation (e.g. radiochemical synthesis), laboratory operation (e.g. release testing), and storage of approved components, including containers and closures, can be located in the same room. (Part B, chapter 3a) Air quality should be adequately controlled to limit the presence of microorganisms and particulate Mather. (Part B, chapter 3b).	3.1 Suitable for the intended activities and not presenting any hazard to the quality of the product. Appropriately designed, built, used, maintained and upgraded, ensuring that they are suitable for the intended activities Reduce risk for cross contamination Adequate measures for pest control Washing and cleaning should not be a source of contamination	Designed, built and maintained so that they do not bear any negative impact on or represent any hazard to the product, personnel or immediate surroundings. Radiopharmacies may prepare a wide variety of RP, often in the same session, and the batch size may be 1 vial and subsequent numbers of patient doses may be low. Radiation safety of operator must be reflected in the design and control of the equipment (Chapter 2)

		Aseptic workstation Grade A in grade C which may be in a grade D environment without further locks and changes of clothing.	Production, storage and quality control areas should be accessible by authorised persons only. Environmental conditions should be defined and monitored. Production areas should allow for segregation of activities. Separation of areas for specific dosage forms should be considered. Dedicated rooms for hazardous products	
Documentation	Chapter 4	Specifications for components and radiopharmaceutical container and closures	4.3 documentation for extemperaneously prepared products - minimum requirements	
Production	Chapter 5		5.2 Exemption: preparation for individual patient not based on written instruction 5.9 release of reprocessed or recovered products solely based on the decision of the Responsible Person	
Quality Control	Chapter 6	Part B chapter 5i: reserve sample from the batch, to permit a repeat quality control Part B chapter 7: sterility testing need not be completed before release	6.1 extent of quality control tests should take into account stability information and physical properties and should be defined on the basis of a risk assessment 6.4 raw materials testing should comply with pharmacopoeia, if no standard exists, the method should be validated Risk assessment: identity of the container – reference to batch certificates only when the reliability of the manufacturer was verified	Chapter 3-3 Starting materials (kits) responsibility of kit manufacturer
Contract Manufacture and Analysis	Chapter 7	(not included)	7.1 in an emergency, an individual extemporaneously prepared medicinal product may be obtained without a written contract. This	

			should be an exceptional occurrence.	
Complaints and Product Recall	Chapter 8	(not included)		
Self Inspection	Chapter 9	(not included)		
Sterile Medicinal Products	Annex 1 Aseptic production: requirement media fill twice a year Clothing for the cleanroom classes Clean room classes and limits for particulate matter and microorganisms.	Part B Chapter 5g: Operators can qualify for aseptic processing by performing media fill runs. Should complete three runs successfully and should be re-qualified periodically. Chapter 1: personnel should appropriately apply aseptique techniques throughout the handling of radiopharmaceuticals for injection, including the radiolabeling of kits. This implies the use of special clothing (masks, sterile gloves), sterile vials sterile syringes, sterile needles and sterile diluents, and that the work is done in a well-planned and expedient way.	Annex 1 to PE 010-03 Additional rules for terminally sterilised and aseptically prepared products 12. Media fill simulations periodically Clean room classes A-D 21. background environments of lesser grade may be acceptable if based on a documented risk assessment 41. different products can be handled in one room at the same time, if justified based on documented risk assessment 65. quality control: if starting materials themselves are licensed medicinal products then it is not usually necessary to test these before use. 66. preparations for a single patient: no end product testing is required (except for radiopharmaceuticals) 67. The extent to which […] quality control tests are performed should be defined on the basis of risk assessment 69. Microbiological analysis is not necessary on each batch. Alternatively a regular programme of microbiological analysis of the units produced over a certain period […] may be acceptable. 81. Recommended frequencies of physical and microbiological	Chapter 3-8 Monitoring of environment and personnel during compounding of radiopharmaceuticals is essential in defining the quality of the final preparation irrespective of the origin of the kits and any material used in the preparation. The frequency of environmental monitoring should reflect the specific risk of the preparation concerned. When a sterile preparation is to be obtained and terminal sterilisation for sterile filtration is not possible, all starting materials have to be sterile. Components of the equipment that come in direct contact with the preparation should be disposable or reused after a validated cleaning procedure is performed. Chapter 3-2 The use of starting materials with acceptable, low degree of microbial contamination is recommended, irrespective of whether the final product is terminally sterilised or sterile filtered. Bioburden and bacterial endotoxin levels of starting materials are important factors of the successive operations and must be kept at a low level. Sterilisation should be considered.

			monitoring (less than Annex 1 EU-GMP guideline)	
Radiopharmaceuticals	Annex 3	Radiation protection – sometimes opposite requirements Production of radionuclide precursors: cyclotron or reactor = non-GMP	Parts of Annex 1 (rf. above)	Provisions for the production of radionuclide precursors (Chapter 3-1) Generator,
Miscellaneous				Kit-based RP If the instructions given by the marketing authorisation holder are not strictly followed or if one or more components used for the preparation do not have a marketing authorisation, risk assessment must be undertaken and documented. It is the responsibility of the radiopharmacy/compounding unit to prove that the quality of the final preparation is suitable for human use. Labelling instructions are given

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Berlin, im April 2012