Chapter

Quality in Non-Licensed Radiopharmaceutical Products: Are We Achieving the Goal?

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Abstract

Radiopharmaceutical compounds, considered a special group of medicines, can be prepared outside the marketing authorisation track. Small-scale preparations at non-commercial sites thereby represent an important segment, however a lack of harmonisation in the regulation leads to extreme differences in the application and availability of radiopharmaceuticals across Europe. A number of guidelines and guidance documents have been issued by European Association of Nuclear Medicine (EAMN), Pharmaceutical inspection convention (PICs), European Directorate for the Quality of Medicines & HealthCare (EDQM) to achieve a good radiopharmacy practice for small-scale preparation. Nevertheless, in the case of non-licensed radiopharmaceuticals their consideration as magistral formulas, in some countries, makes it possible to waive regulatory inspections aimed to ensure those good practices enforcement. Moreover, special attention should be put on the quality assurance process for non-licensed starting materials, given that the final radiopharmaceuticals quality chiefly depends on it. This paper (chapter) will provide an insight into the quality standards applicable to starting materials, such as supplier qualification control, starting material re-test period, etc. in order to raise for discussion about how best to achieve a proven quality, efficacy, and safety for our radiopharmaceuticals (licensed or non-licensed).

Keywords: non-licensed, good radiopharmacy practice, magistral formulas, quality assurance process

1. Introduction

During the '80s radiopharmaceuticals were considered as tracers used in hospital centres under the responsibility of a person with a sound knowledge in the safe use of radiation. It was in 1989 when radiopharmaceuticals were considered for the first time in the European Union as medicinal products after entry into force the Council Directive 89/343/EEC [1]. In this Directive was stated the first official radiopharmaceutical definition as:

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

Radiopharmaceuticals are used in major clinical areas for diagnosis and therapy. They usually have no pharmacologic effects, as they are used in tracer quantities. Consequently, there is no dose–response relationship, which thus differs

significantly from conventional medicinal products. Radiation is an inherent characteristic of all radiopharmaceuticals, and patients always receive an unavoidable radiation dose. In the case of therapeutic radiopharmaceuticals, radiation is what produces the therapeutic effect.

The manufacturing and handling of radiopharmaceuticals is potentially hazardous. The level of risk depends in particular upon the types of radiation, the energy of radiation and the half-lives of the radioactive isotopes. The facilities and procedures for the production, use, and storage are subject to licencing by national and/or regional authorities. This licencing includes compliance both with regulations governing pharmaceutical preparations and with those governing radioactive materials.

Considering the special nature of radiopharmaceuticals, strict adherence to conventional good manufacturing practices is not possible in many scenarios where radiopharmaceuticals are handled. It is necessary to balance aseptic handling practices (patient safety) with radiation protection practices (worker safety) complying with the current *As Low As Reasonably Achievable* (ALARA) requirements. Moreover, a demanding technical difference and challenge is that in most cases, diagnostic radiopharmaceuticals need to be prepared, controlled and used within a short time of a few hours or even minutes due to the physical half life of the radionuclides.

Specific guidance is available on adaptations to the conventional regulatory framework to address challenges of the preparation of radiopharmaceuticals.

2. Medical uses of radiopharmaceuticals

A radionuclide may decay by emitting different types of ionising radiation: alpha (α), beta (β-), positron (β+) and gamma (γ) radiation.

Depending on the radiation characteristics of the radionuclide, the radiopharmaceutical is used either for diagnosis or for therapy. Diagnostic radiopharmaceuticals should decay by gamma emission like Technetium-99 m (99mTc), Iodine-123 (123I) and Galium-67 (67Ga) or positron emission like Fluorine-18 (18F), Oxygen-15 (15O), Carbon-11 (11C), Zirconium 89 (89Zr) and Gallium 68 (68Ga) and never emit alpha particles or even beta particles.

On the other hand, therapeutic radiopharmaceuticals should decay by particulate decay (alpha or beta) since the intended effect is in fact radiation damage to specific cell, examples of β -emitters are Rhenium-186/Rhenium-188 (186Re/188Re), Strontium-89 (89Sr), Lutetium-177 (177-Lu),Iodine-131 (131-I) and Yttrium-90 (90Y) and of therapeutic α-emitters are Actinium-225 (225Ac), Bismuth-213 (213Bi) and Astatine-211 (211At).

Moreover, there is an emerging field of nuclear medicine named theranostics (Therapeutics and diagnostics), that involves diagnostic and therapeutic agents to target diseased cells and tissues. The use of targeting molecules labelled either with diagnostic radioisotopes and with therapeutic isotopes enables a more complete approach to patient management, because the diagnosis can then serve several simultaneous functions: assessing disease, monitoring and selection for therapy. The prospects of identifying the disease and orienting treatment, provide an advance level in precision medicine.

One of the most common examples of theragnosis in nuclear medicine is the use of Gallium 68(68Ga) as a diagnostic radiopharmaceutical, followed by therapy with radionuclides such as Lutetium 177 (177-Lu) to label the same molecule in the context of personalised therapy.

3. Radiopharmaceutical's dosage forms. Alternative methods to control sterility in radiopharmaceuticals

Radiopharmaceuticals are medicinal products on prescription that can be delivered orally (in pill form), intravenously (injected into a patient's vein) or interstitially (inserted into a cavity in the body). The intravenous route of administration is the most used in Radiopharmaceuticals application. According to the European Pharmacopoeia monograph regarding Radiopharmaceutical preparations (01625) [2], these products must be sterile as stated in the following extract.

"*Radiopharmaceutical preparations for parenteral administration comply with the test for sterility. They must be prepared using precautions designed to exclude microbial contamination and to ensure sterility. The test for sterility is carried out as described in the general method (2.6.1).*" [3].

Moreover, the pharmacopoeia also considers the specific nature of radiopharmaceuticals, as specified in this other extract.

"Special difficulties arise with radiopharmaceutical preparations because of the short half-life of some radionuclides, the small size of batches and the radiation hazards. In the case that the monograph states that the preparation can be released for use before completion of the test for sterility, the sterility test must be started as soon as practically possible in relation to the radiation."

With the conventional sterility method (2.6.1) [3] the portions of the media should be incubated for 14 days. Though the test must be started as soon as practically possible in relation to the radiation, it will take several days to achieve a safe level of exposure. This means that sterility testing results would be available around three weeks after the radiopharmaceutical preparation. Consequently, the outcomes of the tests when following this method seldom enable proactive corrective actions to be taken in case a lack of sterility is detected.

Alternative methods for control of microbiological quality have been described in European Pharmacopoeia (5.1.6) [4]. They have shown potential for real-time o near real-time results with the possibility of earlier corrective action. Although this pharmacopoeia chapter is published for information, these new methods, if validated and adapted for routine use can also offer significant improvements in the quality of testing.

Similarly, USP has another monograph (1071) [5] where the following extract can be found.

"Rapid microbial tests for release of sterile short-life products: a risk-based approach".

In this chapter, positron emission tomographic (PET) products are mentioned as an example where these rapid methods could be applied.

"It is widely recognized that the current growth-based sterility tests with an incubation period of at least 14 days are not suitable for products with a short shelf-life or for products prepared for immediate use, which are usually infused into patients before the completion of the test (1). These short-life products include compounded sterile preparations (CSPs), **positron emission tomographic (PET) products***, and cell and gene therapies, which require a new generation of risk-based approaches that include rapid microbial tests".*

The information provided in these pharmacopoeia chapters may be used as a supplement or as an alternative microbiological method and to give guidance on validation of the chosen method. It is neither the intention to recommend one method over another, nor to provide an exclusive list of alternative methods that can be used.

Rapid microbial tests described in USP (1071)

- Adenosine triphosphate bioluminescence
- Flow cytometry
- Isothermal microcalorimetry
- Nucleic acid amplification
- Respiration
- Solid phase cytometry

Alternative methods for control of microbiological quality described in Ph. Eur 5.16

There are 3 major types of determination specific to microbiological tests:

1. **Qualitative tests for the presence or absence of micro-organisms**:
   - Tests based on bioluminescence
   - Solid phase cytometry
   - Gas detection or autofluorescence
   - Nucleic acid amplification techniques (NAT) (2.6.21) may also be used for the detection of mycoplasmas (2.6.7)
2. **Quantitative tests for enumeration of micro-organisms:**
   - Autofluorescence
   - Flow cytometry
   - Direct epifluorescent filter technique (DEFT)
   - Solid phase cytometry
3. **Identification tests**
   - Biochemical and morphological characterisation

Table 1.
List with alternative methods of microbiological quality described in pharmacopoeia European and USP.

In both chapters, European Pharmacopoeia (5.1.6) [4] and USP monograph (1071) [5], it is stated that risk analysis tools may be used to determine which alternative method is to be implemented as well as to balance user requirement specification including time to result, specificity, limit of detection (LOD), sample size, and product attributes. The microbiological alternative methods proposed in European Pharmacopoeia and USP are described in **Table 1**.

4. Types of radiopharmaceutical marketing authorisations

Licensed radiopharmaceuticals manufactured under GMP requirements.

In the European Union, radiopharmaceutical compounds are considered a special group of medicines. Their manufacturing/preparing and uses are regulated by directives and regulations that must be adopted by Member States. (Directive 2001/83/EC [6] and Regulation (EC) No 726/2004 [7]).

For a radiopharmaceutical to be available on the market, sold and marketed, it needs to have a marketing authorisation. The marketing authorisation application must provide evidence of the efficacy, safety, and quality of the radiopharmaceutical. When applying for a marketing authorisation for a radiopharmaceutical, the marketing authorisation application is submitted to a regulatory authority, which will assess the medicinal product's pharmaceutical and chemical quality, efficacy, and safety, as well as its risk–benefit ratio.

In the EU, there are four types of marketing authorisation application procedures. These procedures can be found in European Medicines Agency (EMA) website [8] in its section devoted to medicine for human use marketing authorisations:

- National procedure: Used when applying for a marketing authorisation in one individual EU Member State, Norway, Iceland, and Liechtenstein.

- Centralised procedure: The centralised procedure allows manufacturers to submit a single Market Authorization Application (MAA) to the European Medicines Agency (EMA) who is responsible for the scientific evaluation. Once granted by the European Commission, the centralised marketing authorisation is valid in all European Union (EU) Member States, Iceland, Norway and Liechtenstein.

The centralised procedure is **compulsory for:**

- *Human medicines containing a new active substance to treat:*
  - *human* immunodeficiency *virus (HIV) or acquired immune deficiency syndrome (AIDS);*
  - *cancer;*
  - *diabetes;*
  - neurodegenerative diseases;
  - auto immune and other immune dysfunctions;
  - viral dise*ases.*
- *Medicines derived from biotechnology processes, such as genetic engineering.*
- *Advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines.*
- *Orphan medicines (medicines for rare diseases).*
- *Veterinary medicines for use as growth or yield enhancers.*

It is optional for other medicines:

- *Containing new active substances for indications other than those stated above.*
- *That are a significant therapeutic, scientific, or technical innovation.*
- *Whose authorisation would be in the interest of public or animal health at EU level.*

Today, the great majority of new, innovative medicines pass through the centralised authorisation procedure in order to be marketed in the EU.

If a company wishes to request marketing authorisation in several EU Member States for a medicine that is outside the scope of the centralised procedure, it may use one of the following routes, as also clarified in the EMA website:

- Decentralised Procedure: The procedure for authorising medicines whereby a medicine that has not yet been authorised in the EU can be simultaneously authorised in several EU Member States.

- Mutual Recognition Procedure: The procedure for authorising medicines whereby a marketing authorisation granted in one Member State can be recognised in other EU countries.

In case of Radiopharmaceuticals, that are used extensively to treat people with cancer, centralised procedure will be the proceeding to be followed.

4.1 Radiopharmaceuticals within a clinical trial

On the other hand, the Radiopharmaceuticals can be used for research and development. All requirements to apply in Europe for a clinical trial are stated in *EudraLex - Volume 10 -* **Clinical trials guidelines** *Volume 10 of the publication "The rules governing medicinal products in the European Union"* [9].

The following four circumstances are possible for the use of Radiopharmaceutical within a clinical trial:

- Licensed radiopharmaceutical products used within their authorised indications,

- Licensed radiopharmaceutical products used outside their authorised indications,

- Radiopharmaceuticals having established clinical use that are prepared in accordance with approved regulations and meet approved quality requirements (e.g. as described in a monograph of a pharmacopoeia),

- New radiopharmaceuticals or tracer agents outside the previous categories.

4.2 Small scale preparations of radiopharmaceuticals

Radiopharmaceuticals may be prepared at small scale in healthcare establishments, and they may also be prepared outside the marketing authorisation track.

There are various types of radiopharmaceuticals prepared in healthcare establishments as it is described in PIC/S (Pharmaceutical inspection convention, pharmaceutical inspection co-operation scheme) [10] among which can remark:

- Sterile products with a marketing authorisation which are aseptically prepared in the healthcare establishment. These are typically used for routine diagnostic purposes in nuclear medicine and include:

- Technetium- 99 m radiolabelled ligands obtained by the combination of the kit component with [99mTc] pertechnetate from a radionuclide generator.

- Radionuclide precursors with a marketing authorisation, for example Yttrium-90 which are used as starting materials for synthesis.

- Sterile products without a marketing authorisation which are synthesised, radiolabelled, purified and formulated for diagnostic or therapeutic use.

- Oral products with marketing authorisation which are prepared as capsules or solutions which the patient takes for diagnosis or therapeutic. Use (e. g. Iodine-131 for thyroid treatment).

5. Preparation or manufacturing of radiopharmaceuticals?

The difference between radiopharmaceutical preparation and manufacture is a sensitive issue which calls for a consensus that, it seems not exist at present.

The following definitions for preparation and manufacturing can be found in the GMP Annex 3 [11]:

"Preparation: handling and radiolabelling of kits with radionuclide eluted from generators or radioactive precursors within a hospital. Kits, generators and precursors should have a marketing authorisation or a national licence".

"Manufacturing: production, quality control and release and delivery of radiopharmaceuticals from the active substance and starting materials".

As per the extract above, it becomes apparent that in a preparation, products with marketing authorisation should be used. Provided that the summary of product characteristics (SPC) instructions is followed, the ultimate responsibility for the radiopharmaceutical preparation with respect to its safety, quality, and efficacy, over its shelf live lies with the marketing authorisation holder (MAH). However, this requirement is not remarked in the case of manufacturing.

By contrast, if we regard the Pharmacopoeia European monograph (5.19) Extemporaneous preparation of radiopharmaceuticals [12], the following definition is stated:

"The preparation of radiopharmaceuticals is considered as a process involving some or all of the following steps: purchase of materials and products, production of radionuclides for radiolabelling, radiolabelling, chemical modification and/or purification, formulation, dispensing of the pharmaceutical form, sterilisation, analytical control, packaging, labelling and release. Drawing patient doses for immediate application (e.g., from a multidose vial) is considered as part of clinical practice, and not part of the preparation of Radiopharmaceuticals."

As can be seen in the pharmacopoeia definition, the use of authorised materials and products is not a requirement. From this perspective, preparation and manufacturing processes could seem fairly similar, since purification and sterilisation steps are also encompassed within them. However, as it is stated in Pharmacopoeia European monograph (5.19), the manufacture of radiopharmaceuticals and investigational medicinal products should be covered by existing regulation (authorisation of any competent authority) and a pharmaceutical preparation definition would include all the preparations with licensed and non-licensed products. Additionally, the European Pharmacopoeia monograph 2619 [13] differences two categories, extemporaneous and stock preparations as it can be seen in the following extracts:

"Pharmaceutical preparations are medicinal products generally consisting of active substances that may be combined with excipients, formulated into a dosage form suitable for the intended use, where necessary after reconstitution, presented in a suitable and appropriately labelled container."

"Pharmaceutical preparations may be non-licensed by the competent authority, or unlicensed and made to the specific needs of patients according to legislation. There are 2 categories of unlicensed pharmaceutical preparations:

- extemporaneous preparations, i.e., pharmaceutical preparations individually prepared for a specific patient or patient group, supplied after preparation.

- stock preparations, i.e., pharmaceutical preparations prepared in advance and stored until a request for a supply is received."

On the other hand, we cannot overlook that most radiopharmaceutical preparations are used for parenteral administration, and therefore required to be sterile. Then, if we consider the *EMA guideline on the sterilisation of the medicinal product active substance, excipient, and primary container*, [14] it might seem that whenever a sterilisation procedure has to be applied, it will be considered as a manufacturing process according to the following extract:

"Sterility is a critical quality that cannot be assured by testing, it needs to be assured by the use of a suitably designed, validated and controlled manufacturing process".

Therefore, this consideration seems to contradict the previous pharmacopoeia extracts where the sterilisation process was included in the scope of the preparation definition.

Notwithstanding the difficulties to get an official consensus on the definitions of preparation and manufacturing, there should be an agreement on who bears the final responsibility in them:

- In the event licensed products were used, the responsibility would lie with the marketing authorisation holder (MAH) as long as the summary of product characteristics (SPC) instructions is followed. If these instructions include the need to apply sterilisation, the responsibility on the sterilisation process would also lie on the MAH.

- Otherwise, whenever non-licensed products or licensed products not compliant with SPC instructions were used, the final responsibility would always rest with the Chief Radiopharmacist who prepares/manufactures them.

6. Scientific guidelines

As is stated in the EMA website [8] "*The European Medicines Agency's Committee for Medicinal Products for Human Use prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare marketing authorisation applications for human medicines. Guidelines reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives".*

These guidelines are complementary to European Pharmacopoeia monographs and chapters, since as detailed in the directive 2001/83 EC (annex I) [6] with respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

The catalogue of guidelines is categorised according to the Common Technical Document (CTD) [15] when they concern general issues and include the guidelines that are globally harmonised through the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The Guideline on Radiopharmaceuticals [16] issued by EMA Committee for human medicinal products provides information about specific requirements for radiopharmaceuticals in applications for both marketing and clinical trial authorisations.

Altogether, regulatory authorities and industry prepared ICH scientific guidelines as shown in **Table 2**.

However, CHMP scientific guidelines are just issued by the European Medicines Agency's Committee for Medicinal Products for Human Use.

In addition to the application of the mentioned guidelines, the manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use and with the principles and guidelines on GMP, published by the commission in the rules governing medicinal products in the European Community, Volume 4 [17]. In particular, the EU GMP annex 3 [11] specifically addresses some of the practices, which may be specific for radiopharmaceuticals.

Furthermore, there are also other guidelines published whose main objective is to harmonise inspection procedures worldwide by developing common standards in the field of GMPs and by providing training opportunities to Inspectors. They are issued by The Pharmaceutical Inspection Co-operation Scheme (PIC/S) who is a non-binding, informal co-operative arrangement between Regulatory Authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use. Particularly, the annex 3 of PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments is devoted to Radiopharmaceuticals [10].

Similarly, EDQM has published in the European Pharmacopoeia, the monograph 5.19 Extemporaneous preparation of Radiopharmaceuticals [12]. Although this monograph is only for information, it covers guidance for preparing "kit-based preparations (from licensed and unlicensed kits) and unlicensed preparations containing radionuclides for positron emission tomography (PET), single photon emission computed tomography (SPECT) or for therapeutic applications".

In the USP several monographs can also be found regarding radiopharmaceuticals preparation, such as USP (825) [18] radiopharmaceuticals preparation, compounding, dispensing and repackaging or USP (823) [19] Positron emission tomography drugs for compounding, investigational, and research uses.

Besides, other "for information" guidelines can be mentioned. For instance, a guideline to achieve a good radiopharmacy practice for small-scale preparation was issued by The European Association of Nuclear Medicine (EANM) [20]. This is a professional non-profit medical association that facilitates communication worldwide among individuals pursuing clinical and research excellence in nuclear medicine.

In conclusion, many guidelines and guidance documents have been issued to foster good radiopharmacy practices for licensed or not licensed radiopharmaceuticals in both large and small-scale preparation.

Region	Regulatory authorities	Industry
Europe	EMA	EFPIA
USA	FDA	PhRMA
Japan	MHLW	JPMA

Table 2.
Summary of the parties involved in the ICH guidelines development.

7. Radiopharmaceuticals preparation outside the marketing track in the European Union

In the European Union (UE), the community code relating to medicinal products for human use is regulated by the Directive 2001/83/EC [6] as amended. This Directive has to be adopted by Member States. The rate and extent of adoption and interpretation of the Directive varies among countries. Each Member State may introduce changes, provided the general scope and limits of the directive is maintained.

In this way, several European Member States have set up a regulatory framework in which radiopharmaceuticals for routine use can be prepared on site without the requirements of a marketing authorization. These exemptions flow from the definitions in Article 3 of Directive 2001/83/EC [6], the so-called magistral and officinal formulae, and from Article 5(1) of Directive 2001/83/EC aimed to fulfil special needs.

The European Court of Justice. Document 62013CJ0544 and Judgement of the Court (Third Chamber) of 16 July 2015 has clarified both situations of Articles 3 and 5 [21].

Considering article 3, for "magistral formulae" defined as "any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient". The European Court of Justice specified that "[such a preparation] must of necessity be prepared on the basis of a prior prescription issued by a professional person qualified to do so". This prescription must, in addition "be 'for an individual patient'" and "that patient must be identified before the medicinal product is produced and it must be produced specifically for that patient". It was also stated that "the exception provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market, or which is unavailable on that market", clearly excluding competition with licensed medicinal products.

Similarly, by virtue of Article 5(1) of Directive 2001/83 [6], to fulfil special needs, exclude from the provisions of that directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility. In that regard, the court has held that it is apparent from the conditions as a whole set out in that provision, read in the light of the fundamental objectives of that directive, and in particular the objective of seeking to safeguard public health, that the exception provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market (see, to that effect, judgement in Commission v Poland, C-185/10, EU:C:2012:181, paragraphs 29 and 36).

United Kingdom (UK) is the clear example of applying the exception of art 5(1) of the Directive 2001/83/EC [6], despite after Brexit is no longer part of the European Union (UE). The regulation 167 of the Human Medicines Regulations 2012 sets out the exemption from the requirement for a medicinal product, placed on the market in the UK to hold a marketing authorisation. Additionally, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued the MHRA Guidance Note 14 called "The supply of unlicensed medicinal products ("specials") [22].

In some Member States (Austria, Belgium etc..) the preparation of PET radiopharmaceuticals could be considered, in many situations, as magistral formulas since they are prepared in accordance with a medical prescription for an individual

patient. The preparation of radiopharmaceuticals as magistral formulae is not covered under the Directive 2001/83/EC [6], therefore its legislation falls under the responsibility of each Member State.

In Germany, PET radiopharmaceuticals can be manufactured according to the requirements set in article 13(2b) of the Medicinal Products Act (Arzneimittelgesetz, AMG) where it is stated that "*a person who is a doctor or dentist or who is otherwise authorised to practise medicine on humans does not require a licence according to paragraph 1, insofar as the medicinal products are manufactured under his direct professional responsibility for the purpose of personal use on a specific patient*". However, it is important to note that the compliance with the Medicinal Products Act is controlled by the Federal States, coming along with the acceptance of varying practices by different state authorities. Hence, there is currently a lively discussion in the nuclear medicine community about minimum standards for this production, though the use of radiopharmaceuticals with marketing authorisation is preferential.

By contrast, in Spain, the preparation of radiopharmaceuticals cannot be considered as magistral formulae since they must be prepared with legally recognised action and indication substances as stated in Royal Legislative Decree RDL 1/2015. Therefore, the only way to prepare PET radiopharmaceuticals outside the marketing authorisation track would be under the regulatory framework of article 47.1c in Real Decree (RD) 1345/2007 on the marketing authorization procedure in medicines for human use [23]. This Decree completes the RDL 1/2015 [24], which is the transposition of Directive 2001/83/EC [6]. The article 47.1.c in the RD 1345/2007 [23] establishes the following criteria:

The marketing authorisation for PET radiopharmaceuticals will not be required, whenever they are prepared in an approved radiopharmaceutical unit under the supervision and control of a radiopharmaceutical specialist, provided that they meet the following requirements:

1. They are entirely prepared and used in the authorised radiopharmacy units with non-profit use and in centres linked to the National Health System.

2. They are substances used in clinical research, or medicines that the Spanish Agency for Medicines and Medical Devices (AEMPS) considers satisfying the guarantees of quality, safety, efficacy, identification, and information, and that are prepared in appropriate facilities.

Beyond the lack of alignment regarding the definition of radiopharmaceuticals preparations analysed above, differences can also be found with respect to the requirements that manufacturers have to comply with in their preparation. The following examples depict this situation:

- In United Kingdom as is stated in MHRA Guidance Note 14, [22] "the manufacturer or assembler of "specials" must hold a Manufacturer's "Specials" Licence granted by the Licencing Authority." Furthermore, it is also said that "the manufacturing/assembly site and its operations will be inspected for compliance with Good Manufacturing Practice (GMP) and the conditions of the licence".

- In Spain the situation seems to be fairly like UK, the manufacturer must apply the Spanish Medicines Agency (AEMPS) for a certificate of compliance with requirements and the sites operations will be inspected for compliance with Good Manufacturing Practices (GMPs).

- In the rest of the Member States there are different degrees of compliance with Good Manufacturing Practices (GMPs). In some countries as Germany full adherence to GMPs is required, while in other countries such as Italy special or adapted GMPs are enforced. Finally, there are other countries where this compliance is not clearly specified.

Summarising, there are different ways to carry out the radiopharmaceuticals small scale preparation outside the marketing authorisation track, depending on the national legislation in each Member State. Hence, a cornerstone of the radiopharmaceutical's preparation might currently be the lack of harmonisation at European level, especially regarding the quality standards applicable to these preparations.

Nevertheless, leaving aside the lack of harmonisation among countries, special attention shall be drawn to the achievement of the highest standard quality radiopharmaceutical preparations. It is a fact that, as a rule, this goal is accomplished in the manufacturing processes for medicinal products by applying GMPs. For sure, these practices should consider the special nature of radiopharmaceuticals balancing aseptic handling with radiation protection. Besides, authorities should ensure that manufacturers in their territory are subject to routine GMP inspections.

In the field of clinical trial this goal is on its way thanks to the new Regulation 536/2014 [25] repealing the Directive 2001/20/EC. This regulation will achieve the harmonisation between Member States, through the creation of a uniform regulatory framework for the authorization of clinical trials. It is to be noted that European Regulations are not transposed by the European Members but directly applied. Therefore, European Member States shall be compliant with this regulation.

The Regulation 536/2014 [25], in the case of radiopharmaceuticals used in clinical trials stablishes differences between therapeutic and diagnostic radiopharmaceuticals. While therapeutic radiopharmaceuticals are considered as any other medicinal product used in a Clinical Trial, regarding diagnostic radiopharmaceuticals substantial changes are introduced by the following article (Art. 61.5.b of Regulation 536/2014):

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

Based on the analysis of this article in conjunction with other relevant ones of this regulation it is observed that:

1. The authorization for manufacturing and import for the radiopharmaceuticals included in the art. 61.5.b is not needed.

2. GMPs to produce the Radiopharmaceuticals included in the exception of art. 61.5.b seems not to be needed. Because of Regulation 536/2014, two new legislation documents in relation to GMP have been released: (1) Directive 2017/1572 [26], the new GMP Directive that repeals the old GMP Directive 2003/94; and (2) Regulation 2017/1569 [27], a new GMP Regulation for IMPs (Investigational Medicinal Products) that does not apply to those radiopharmaceuticals included in art. 61.5.b of Regulation 536/2014. However, apparently contradicting the previous exception, this regulation remarks that Member States could carry on regular inspections to ensure subject safety and reliability and robustness of the data generated in the clinical trial, as detailed in the extract below of the Art. 61.6 in the mentioned Regulation 536/2014:

"Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections."

3. Simplified labelling of diagnostic radiopharmaceuticals used as investigational medicinal products (IMPs) and auxiliary medicinal products (AMPs)

It should be noted that this exception for diagnostic radiopharmaceutical is only in the context of a clinical trial where the number of patients and the length of study is limited. Moreover, art 61.6 of Regulation 536/2014 leaves open the possibility for each Member State of having regular inspections with their specific requirements.

This situation shall be seen as totally different from the small-scale radiopharmaceutical preparation on a routine basis, where bypassing the compliance with good manufacturing practices affecting the quality of the radiopharmaceuticals could have an impact on a much larger number of patients in the day-to-day usage.

8. Starting materials for the PET radiopharmaceuticals preparations

The definition of a starting material is depicted in part II of Good Manicuring Practices (GMPs) [28] as shown in the extract below:

"An Active Substance Starting Material is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance. An Active Substance Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. Active Substance Starting Materials normally have defined chemical properties and structure".

In case of the PET Radiopharmaceutical preparations, the main starting material is the chemical precursor whose definition is stated in the European Pharmacopoeia monograph 2902 named Chemical Precursors for Radiopharmaceuticals Preparations [29] as follows:

"Chemical precursors are non-radioactive substances obtained by chemical synthesis for combination with a radionuclide".

In this monograph a risk assessment is requested whenever the radiopharmaceutical preparation is required for special needs of individual patients, provided that non individual monograph for the precursor is available. Likewise, differences between diagnostic use versus therapeutic use as well as the frequency of use shall be taken into account for the risk assessment. These indications are fully described in the paragraph below extracted from monograph 2902:

"Where a chemical precursor not described in an individual monograph of the European Pharmacopoeia is used in a radiopharmaceutical preparation prepared for the special needs of individual patients, the need for compliance with this general monograph is decided in the light of a risk assessment.

This risk assessment takes account of:

- the quality of the chemical precursor and the information available for quality evaluation.
- any further processing after radiolabelling (which may or may not include purification before administration to the patient).
- the amount used to prepare a patient dose (e.g., diagnostic use versus therapeutic use) and the frequency of administration to the patient."

The quality of the chemical precursors is critical to ensure the final quality of the radiopharmaceutical product. These precursors are used in radiolabelling reactions for the preparation of the radioactive pharmaceutical ingredients (APIs) that are not isolated and/or fully analysed before incorporation in the final radiopharmaceutical preparation. For this reason, according to the Guideline on Radiopharmaceuticals [16] they should satisfy the Note for Guidance on Summary of Requirements for Active Substances in Part II of the Dossier [30].

It is relevant to remark that during the radiopharmaceutical quality dossier preparation to be submitted to the relevant authorities, the information on chemical precursors including those for synthesis of PET radiopharmaceuticals may be presented in a separate Section 3.2.S following the requirements of the Common Technical Document (CTD). This is stated in the European Commission Document Volume 2B Notice to Applicants Medicinal products for human use [15]. This approach must be followed for both marketing authorisation (MAA) and clinical trial authorization (CTA) applications.

In particular, the module 3 of the CTD covers chemical and pharmaceutical data including data for biological/ biotechnological products. This module has two parts: drug substance and drug product part. In the case of the chemical precursor of the radiopharmaceutical preparation, it should comply with the drug substance requirements section.

The Guideline on Radiopharmaceuticals [16] describes the specific additional information that needs to be submitted in relation to radiopharmaceuticals, when preparing the radiopharmaceutical quality dossier. The following sections included in **Table 3** should be completed:

The information depicted in **Table 3** can be submitted by the applicant to the regulatory authorities following two different procedures:

1. Firstly, according to the current EU Guideline on the ASMF procedure (Active Substance Master File Guideline [31]. The main objective of it, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the Applicant or Marketing Authorisation (MA) holder to take full responsibility for the medicinal product and the quality and quality control of the active substance. In the case of radiopharmaceuticals preparation would be the chemical precursor manufacturer the ASMF holder.

2. Secondly, the applicant could submit the information included in **Table 3**, through the CEP procedure (certificate of suitability of the monograph of the European Pharmacopoeia) that is granted by the European Directorate for the Quality of Medicines (EDQM). It is stated in the Directive 2001/83/EC [6] amended by 2003/63/EC [32] as it is shown in the extract below:

"Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines."

On the contrary, if the applicant did not want to use either of the two previous procedures, all sections could be submitted directly to the regulatory authorities.

3.2.S.1 General Information
• 3.2.S.1.1 Nomenclature
• 3.2.S.1.2 Structure
• 3.2.S.1.3 General Properties
3.2.S.2 Manufacture
• 3.2.S.2.1 Manufacturer(s)
• 3.2.S.2.2 Description of Manufacturing Process and Process Controls
3.2.S.2.3 Control of Materials
3.2.S.2.4 Controls of Critical Steps and Intermediates
3.2.S.2.5 Process Validation and/or Evaluation
3.2.S.2.6 Manufacturing Process Development
3.2.S.3 Characterisation
• 3.2.S.3.1 Elucidation of Structure and other Characteristics
• 3.2.S.3.2 Impurities
3.2.S.4 Control of Drug Substance
• 3.2.S.4.1 Specification
• 3.2.S.4.2 Analytical Procedures
• 3.2.S.4.3 Validation of Analytical Procedures
• 3.2.S.4.4 Batch Analyses
• 3.2.S.4.5 Justification of Specification
3.2.S.5 Reference Standards or Materials
3.2.S.6 Container Closure System
3.2.S.7 Stability
• 3.2.S.7.1 Stability Summary and Conclusions
• 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
• 3.2.S.7.3 Stability Data

Table 3.
Module 3 of common technical document (CTD) drug substance part.

These requirements are mandatory for both clinical trial and marketing authorisation applications, however they should also be compulsory for radiopharmaceuticals prepared outside the marketing authorisation track, regardless of the category to which they belong (magistral formula, special product, etc...). A clear example where this information is required is Spain. Hence, to prepare PET radiopharmaceutical outside the marketing authorisation track under the regulatory framework of article 47.1c in RD 1345/2007 [23], it is always necessary to submit the previously mentioned module 3 of CTD to the regulatory authority (AEMPS). In this way, the quality of the preparation in both chemical precursor and final radiopharmaceutical would be ensured.

It is noteworthy that, as a general rule, the information provided by the chemical precursor manufacturers is very limited. It is usually only submitted the chemical precursor structure, the specification, and some batch results. Obviously, this information should not be considered as sufficient to guaranty the quality of the final product.

Regarding the stability studies, stress testing of the chemical precursor must be performed to identify the likely degradation products, as well as to complete

stability studies to cover storage, shipment, and subsequent use, according to ICH Q 1 A (R2) Stability Testing of new Drug Substances and Products [33]. However, the chemical precursor manufacturer is not obliged to stablish a retest period, but in case no retest period is defined, a statement should be included that the precursor is tested immediately before the drug product manufacture. In case retest period had not been proposed, the radiopharmacy unit would test the chemical precursor before its use. The details on the retest period information should be considered by the drug product manufacturer, in the case under analyse, the radiopharmacy unit.

A relevant problem is that, in most cases, radiopharmacy units are not aware of this fact and even when they knew it, they would not be equipped for performing such tests.

Regarding compliance of GMPs, according to Good Manufacturing Practices Part II: Basic Requirements for Active Substances used as Starting Material [28] the following requirements should be complied:

- The identity of the chemical precursor should be verified at least of each batch.
- Full analyses on at least three batches should be conducted before reducing in-house testing.
- As a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis.
- Reliability of Certificates of Analysis should be checked at regular intervals.

Considering that radiopharmacy units are not usually equipped to fulfil these requirements, the requested tests could be outsourced following the requirements of GMP Chapter 7 Outsourced Activities [34].

Hence, there should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials. Additionally, for all starting materials and critical components, only qualified vendors should be used. Vendor qualification can be established by an audit, by responses to a Quality Assurance questionnaire, or simply based on experience with this supplier (e.g., the hospital pharmacy). In any case, vendor qualification should always be documented.

As we can see, special attention should be devoted to the purity and control methods for all starting materials, reactants, chemicals, reagents, and solvents used in synthesis and purification regardless they are licensed or unlicensed radiopharmaceuticals. Furthermore, it should be stressed that radiopharmaceuticals containing radionuclides of short physical half-life (e.g., PET radiopharmaceuticals), can be released before all results on finished product testing are available, therefore the consistency of all the steps in the production process has a crucial importance.

9. Conclusion

This text aimed to provide an overview on the radiopharmaceutical preparations in the European Union, focusing on the main differences between national laws regarding the non-licensed small-scale preparations, while analysing whether the quality expectations on them are really achieved or not. It went through a recap of the alternative methods to control sterility in radiopharmaceuticals, types of radiopharmaceutical marketing authorisations, differences between preparation and manufacturing of radiopharmaceuticals, available guidelines related to the

quality in radiopharmaceuticals field, radiopharmaceuticals preparation outside the marketing track in the European Union and starting materials quality requirements for PET Radiopharmaceuticals preparations.

The intention was to raise some of the hot topics in the scientific community around the radiopharmaceutical compounds, considered a special group of medicines, that can be prepared outside the marketing authorisation track. In particular, small-scale preparations at non-commercial sites which represent an important segment, despite a lack of harmonisation in the regulation leads to extreme differences in the application and availability of radiopharmaceuticals across Europe.

It is noteworthy, that most radiopharmaceutical preparations are sterile injectable products. As developed along the text, the existing regulation on the manufacture of sterile medicines, shall imply the need of a harmonisation in the European Union regarding the requirements applicable in the small-scale preparation of radiopharmaceuticals, which are currently considered not clear enough. A possible way forward might be the compliance with Good Manufacturing Practices (GMPs) properly adapted to the special nature of small-scale preparation of radiopharmaceuticals.

Moreover, special attention should be put on the quality assurance process for non-licensed starting materials, given that the final radiopharmaceuticals quality chiefly depends on it.

To sum up, the radiopharmacists community should try to achieve a proven quality, efficacy, and safety for our radiopharmaceuticals, regardless if they are licensed or unlicensed products, both in large or small-scale preparations.

Abbreviation list

AIDS	Acquired Immune Deficiency Syndrome
AEMPS	Agencia Española del Medicamento y Productos Sanitarios
AMPs	Auxiliary Medicinal Products
ALARA	As Low As Reasonably Achievable
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File Guideline
CEP	Certificate of suitability of the monograph of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CTA	Clinical Trial Authorization
CTD	Common Technical Document
DEFT	Direct Epifluorescent Filter Technique
EANM	European Association of Nuclear Medicine
EDQM	European Directorate for the Quality of Medicines & HealthCare
EFPIA	European Federation of Pharmaceutical Industries Associations
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GMPs	Good Manufacturing Practices
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IMPs	Investigational Medicinal Products
JPMA	Japan Pharmaceutical Manufacturers Association
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHLW	The Ministry of Health, Labour and Welfare

MHRA	The Medicines and Healthcare Products Regulatory Agency (UK)
NAT	Nucleic Acid Amplification Techniques
PET	Positron emission tomography
PhRMA	Pharmaceutical Research and Manufacturers of America
PICs	Pharmaceutical inspection convention, pharmaceutical inspection co-operation scheme
SPC	Summary of Product Characteristics
SPECT	Single Photon Emission Computed Tomography

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