Challenges in the Small-Scale Preparation of Radiopharmaceuticals - A European Perspective

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Summary
Radiopharmaceuticals (RP) are a special group of drugs often requiring preparation in hospitals on a small scale. They have to be handled in a legal framework that is mainly suited for conventional drugs and manufacture by large drug manufacturers. Especially with the advent of positron emission tomography (PET) using radionuclides with ultra-short half-life, a need for specific regulations has become obvious as current practice in Europe today is highly variable. The main challenges in this respect are preparation standards (Good Manufacturing Practice), quality requirements, regulations for marketing authorization, and training of personnel. A number of initiatives were started to inform European institutions of the specific case of RP. Specific guidelines for the small-scale, non-commercial extemporaneous preparation of RP have been published, and a specialized post-graduate training program on the European level was introduced to offer a unified system to obtain appropriate expertise in the field of small-scale RP preparation. For RP, both due to their short half-life and the often limited clinical indication, the market size is usually very limited. Specific exemptions for clinical trials in addition to routine application of RP are needed to cover patients' needs. A unified European approach for RP would be of great importance to guarantee high standards in the quality and safety of RP, especially for those prepared extemporaneously.

Key Words: Radiopharmaceuticals, European regulations, PET, SPECT, small scale preparation

INTRODUCTION
Radiopharmaceuticals are a very special group of drugs. They contain a radionuclide emitting ionizing radiation that can be detected externally for diagnostic purposes or can serve as a therapeutic tool for treating severe diseases. The great majority of radiopharmaceuticals are applied for diagnostic purposes using gamma cameras for conventional scintigraphy and tomographic imaging, called single photon emission computed tomography (SPECT). Recently, positron emission tomography (PET) has become of increasing importance providing improved sensitivity and resolution. A number of radiopharmaceuticals are prepared and provided by commercial manufacturers and used as such for patient application in the Nuclear Medicine department. However, especially for diagnostic purposes,
a short half-life of the incorporated radionuclide is mandatory to provide low radiation dose to the patient. This makes industrial manufacture and distribution challenging and in some cases impossible. For SPECT application, this has been the case for $^{99m}$Tc-radiopharmaceuticals. Technetium-99m, with a half-life of 6.02 hours, has been the workhorse of Nuclear Medicine for the past three decades. It is eluted from radionuclide generators thereby separated from the parent radionuclide Molybdenum-99 with a half-life of 64 hours, providing sufficient $^{99m}$Tc-radioactivity typically for a period of 1-2 weeks. To allow a variety of applications, radiolabelling kits have been developed for the preparation of different $^{99m}$Tc complexes in simple, straight forward procedures on-site in the Nuclear Medicine department. In most European countries, this practice of kit preparation is not regarded as drug manufacturing or preparation and is performed in the hospital by technologists under the supervision and responsibility of medical doctors.

Especially with the advent of PET as a clinical diagnostic tool and advances in PET-scanner technology (such as image fusion using PET/CT), small-scale preparation of radiopharmaceuticals is beginning to shift from SPECT to PET applications. The most common PET radionuclides are $^{18}$F and $^{11}$C, with even shorter half-lives of only 110 and 20 min, respectively. Even though $^{18}$F-radiopharmaceuticals can be prepared centrally and are then distributed to several clinical centers, this is not possible for $^{11}$C, and many PET centers therefore have not only imaging modalities but also a cyclotron for on-site production of these radionuclides. Another PET radionuclide that has recently gained considerable interest is $^{68}$Ga, which can be eluted from a generator comparably to $^{99m}$Tc (parent $^{68}$Ge, half-life 271 days). The preparation of PET radiopharmaceuticals, however, involves complex chemical synthesis procedures using high amounts of radioactivity and often including complicated isolation and purification procedures, e.g. by high performance liquid chromatography (HPLC). These practices require a high level of knowledge and expertise in the processes and usually involve both radiochemists and radiopharmacists.

Another trend has developed towards new radiopharmaceuticals for therapy. Recent advances in therapeutic applications of radiopharmaceuticals in oncology have seen the development of highly targeted compounds aimed at receptors or antigens. Especially radiometal-labelled peptides and antibodies today are frequently used for treatment of neuroendocrine tumors and lymphomas. They involve the use of beta emitters such as $^{90}$Y and $^{177}$Lu, typically also prepared individually for patients on site involving again chemical synthesis and purification processes performed by specialized radiopharmacists or -chemists.

This article focuses on issues related to the small-scale preparation of radiopharmaceuticals usually for individual patients especially for PET, but also for other applications, not involving simple kit preparations. It deals with the legal, pharmaceutical and technical challenges involved and how they may be solved in a European context.

Legal aspects in the use of short-lived radiopharmaceuticals

Some major legal documents of importance for radiopharmaceuticals are shown in Table 1. The majority of drugs are used in a legal context as “medicinal products”. These are according to Directive 2001/83 (Medicinal Products for human use, (1)): “…prepared industrially or manufactured by a method involving an industrial process…”. In this case, regulations are straightforward, and a marketing authorization, within the European Union (EU) either centralized or on a national basis, is required for use in patient treatment. Radiopharmaceuticals in general fall in this category, i.e. require marketing authorization. This also includes radiolabelling kits, radionuclide generators and radionuclide precursors. The small-scale preparation of radiopharmaceuticals, however, is different, especially for radiopharmaceuticals with a short half-life. One exception is $2-[^{18}$F]fluor-2-deoxy-D-glucose ($^{18}$F-FDG), a PET radiopharmaceutical that is prepared via nucleophilic substitution of a precursor molecule (Fig.1) has a marketing authorization in most European countries and is shipped by commercial producers to the hospitals. $^{18}$F-FDG is by far the most frequently used radiopharmaceutical, making this way possible and also attractive for commercial production. For the majority of PET and other radiopharmaceuticals prepared on a small scale, marketing authorization is usually not available. Applying for marketing authorization is not attractive for a commercial producer and therefore the application of these radiopharmaceuticals has to be seen in another context. This can either be the way of the so-called “magistral” or...
“officinal” preparation as defined in Directive 2001/83 (1). It means the preparation is based either on the prescription of a medical doctor or on a pharmacopoeia monograph and performed in a pharmacy. This is followed in some countries, and the hospital preparation of radiopharmaceuticals on a small scale is based on the pharmacy status of the radiopharmacy unit. In many countries, laboratories especially preparing PET radiopharmaceuticals are situated in university institutes or research laboratories without pharmacy status. Local regulations often do not allow pharmacies to have a licence for radioactivity, prohibiting the handling of radiopharmaceuticals in a pharmacy (e.g. in Germany). The preparation of short-lived radiopharmaceuticals is then either based on a specific local regulation or, in many cases, directly under the responsibility of the medical doctor based on individual patient need. In the first case, specific authorization is given, and institutions are usually controlled by national pharmaceutical inspection schemes. In the second situation, there are often no clear regulations for pharmaceutical inspection authorities and authorization is given based on radiation protection legislation only. In many European countries, this is still the case for local, hospital-based preparation of radiopharmaceuticals.

However, authorities are increasingly becoming aware of this situation, and recent developments indicate that European and national authorities try to find specific solutions allowing the routine use and application of small-scale preparations without having to apply for a marketing authorization or for a specific clinical trial for these radiopharmaceuticals. In Germany, the recent change in the “Verordnung über radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel” (AmRadV) (2) includes the possibility of using radiopharmaceuticals without a marketing authorization or clinical trial status, if they are prepared in a pharmaceutically authorized institution for not more than 20 applications per week. In Italy, a recent change in pharmaceutical legislation (3) includes the possibility to prepare and use “experimental radiopharmaceuticals” without marketing authorization but after applying specific Good Manufacturing Practice (GMP) guidance as outlined in the National Pharmacopoeia. The major concern authorities have regarding these products, however, remains: who controls and defines environmental and training standards of personnel as well as quality standards of the preparation itself? This issue is also a matter of debate among specialists and authorities and is addressed in the following chapters.

**Standards of preparation – GMP**

In general, standards for the preparation of pharmaceuticals are summarized under the term GMP. Directive 2001/83 [4] states that all medicinal products have to comply with the current standards of GMP. In Europe, these GMP rules have legal character as they are issued by the European Medicines Agency (EMEA) and the DG Enterprise& Industry of the European Commission. They are published
online in the Eudralex, a web-based compendium of European pharmaceutical legislation (5). For radiopharmaceuticals, a dedicated Annex (Annex 3) covers specific GMP regulations related to radiopharmaceutical production. It includes specific issues regarding radiation safety in the handling of these drugs and also related to the short half-life, for example allowing the release of the product before all tests are completed (e.g. sterility testing). Just recently, Annex 3 has been revised, taking into account the rapid development of radiopharmaceuticals, especially in the field of PET. It specifically included PET preparation and the requirements regarding radionuclide production, automation and closed procedures. However, Annex 3 is part of the framework of general GMP, intended mainly for industrial, large-scale production. It poses great challenges for the small-scale preparation in a hospital setting. This includes, for example, the requirement of clean room facilities for sterile preparations according to industrial standards, the strict requirement of separation of quality control from production facilities, issues such as vendor qualification or sampling of quality control samples (e.g. for sterility testing), and the involvement of Qualified Persons (QPs) with special training in the preparation of radiopharmaceuticals on an industrial scale.

However, Directive 2001/83 (1), the basis for European GMP as outlined in Eudralex, only has a mandate for the industrial manufacture of medicinal products and does not legally cover the small-scale, patient-individual preparation e.g. in pharmacies. The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) has therefore recently issued a “PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments” (6) that describes a specific GMP intended for hospital preparation of pharmaceuticals. This document only makes a few remarks regarding the special nature of radiopharmaceuticals concerning their short half-life and radioactive nature, but is not at all specific on this topic. The Radiopharmacy Committee of the European Association of Nuclear Medicine (EANM) has released guidelines specifically related to the small-scale preparation of radiopharmaceuticals (7). To differentiate them from “conventional” GMP, they were named “Current Good Radiopharmacy Practice” (cGRPP), despite being essentially based on cGMP. It includes elements regarding Personnel and Resources, Premises and Equipment or Documentation.

The major aim was to achieve a consensus document that specifies the needs for radiopharmaceutical preparations in hospitals and academic institutions, not only for research and clinical trial applications, but also for every day routine nuclear medicine applications. To cover the specific needs, two distinct parts were included: Part A dealing with radiopharmaceuticals prepared from generators and kits (mainly 99mTc-radiopharmaceuticals) and Part B with other radiopharmaceuticals prepared non-industrially on a small scale, mainly but not exclusively for PET applications. Several issues have been addressed, allowing a much better suited interpretation of cGMP for small-scale radiopharmaceutical preparation without impairing quality and safety.

Preparation standards – quality requirements and the European Pharmacopoeia

A major concern for individual patient preparations of pharmaceuticals in general is how quality requirements can be guaranteed when no marketing authorization has been granted. Application for marketing authorization includes submission of detailed data on quality parameters and specifications of the drug. Traditionally, definition of quality standards of certain preparations has always been a main aim of the pharmacopoeia. The European Pharmacopoeia (8) has recently set a focus on PET-preparations and also other issues related to the small-scale preparation of radiopharmaceuticals. This pharmacopoeia has a legal force in the countries that have signed the European Pharmacopoeia convention. It is a publication of the European Council, and radiopharmaceutical monographs are drafted by a dedicated expert group (Group 14). Specific monographs on radiopharmaceuticals can be found on conventional SPECT radiopharmaceuticals including 99mTc, radiiodinated compounds, other diagnostic radionuclides (³²P, ³¹P, ⁵¹Cr, ⁵۰Co, ⁶۷Ga, ¹¹¹In, ⁸¹mKr, ²⁰¹Th, ¹³³Xe) and therapeutic radionuclides (³²P, ⁸⁹Sr). An increasing number of monographs deal with PET radiopharmaceuticals (¹⁸F, ¹¹C, and ¹⁵O labelled). Monographs on radionuclide precursors (radionuclide formulations that are used for radiolabelling or preparation of generators such as ¹³¹I, ¹²³I, ⁹⁹Mo) and also non-radioactive precursors required in the preparation of radiopharmaceuticals were recently added (e.g. Mannose triflate, DTPA, MDP).
Additionally, the European Pharmacopoeia provides definitions of quality standards in a general monograph on radiopharmaceutical preparations as well as general methods for testing including biological tests (sterility, pyrogens, bacterial endotoxins) and limit tests (heavy metals, identification and control of residual solvents) as well as issues on specific dosage forms (parenteral preparations).

If a radiopharmaceutical is described in the European Pharmacopoeia, it not only defines quality parameters, but also renders development and validation of analytical methods, including their validation, unnecessary. It is the reference for authorities to prove that the quality of a radiopharmaceutical is suitable for clinical application and allows preparation of the radiopharmaceutical in a pharmacy.

**Clinical trials and drug development with radiopharmaceuticals**

A major challenge in Europe regarding radiopharmaceutical preparations has been the change surrounding the conduct of clinical trials. This was started with the “Clinical Trial Directive” (9) that introduced a number of general requirements such as standardized documentation including pharmaceutical requirements. A number of additional guidelines followed, e.g. on the chemical and pharmaceutical documentation required (Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials) (10). Directive 2003/94/EG (11) introduced the general requirement for preparation of Investigational Medicinal Products (IMP) according to GMP, forming the basis for issuing a new annex 13 to the European GMP for these preparations. Additionally, a short time later, the legal framework was further tightened by the implementation of Directive 2005/28/EC (12) introducing the requirement of special authorization for the preparation of IMPs for clinical trials. Other legal documents followed, including guidelines for the first use of a new pharmaceutical in man (first in human clinical trial guideline) issued shortly after a severe almost lethal incident with patients in a trial with a monoclonal antibody (13). All these regulations and guidelines have made the use of radiopharmaceuticals within clinical trials much more difficult than before. This is especially challenging as it not only affects clinical trials that evaluate the efficacy or safety of the new radiopharmaceutical itself, but also clinical trials where radiopharmaceuticals are used to monitor efficacy of treatment with other novel drugs or new applications. On the other hand, such applications of radiopharmaceuticals as “biomarkers” have even been recommended by health authorities such as the Food and Drug Administration (FDA) to monitor clinical trials. However, regulations do not take into account the excellent safety profile of radiopharmaceuticals, which are administered in a controlled environment, usually only once, and in concentrations far below any pharmacological doses. One of the few exemptions in this respect is the acceptance of the microdosing concept by the authorities, reducing the requirements for preclinical safety testing when "less than 1/100 of the dose calculated to yield a pharmacological effect of the test ......and at a maximum dose of ≤100 micrograms“ are administered (14). The current complex legal situation concerning clinical trials and radiopharmaceuticals has recently been summarized by the Drug Development Committee of the EANM (15).

**Responsibility and education**

A major challenge in the small-scale preparation of radiopharmaceuticals in the future will be the education and expertise of persons responsible for this type of preparation. For the industrial manufacture of pharmaceuticals in general, the Qualified Person (QP) was introduced with Directive EC 2001/83 (1). QPs for pharmaceutical production in an industrial environment are defined by their professional background (usually pharmacists, in some countries also chemists, biologists or related experts) with appropriate experience and training in quality assurance. Such a professional requirement is not suitable for radiopharmaceutical preparations as it does not take into account the specific knowledge and expertise required for radiopharmaceuticals in particular regarding radioactive nature, the small scale and variety of operations performed. Specialization as hospital pharmacist is also of limited use for similar reasons. Some countries such as Belgium have already recognized this problem and introduced the recognition of the radiopharmacist’s specialization in their national regulations. In some European countries such as Germany, the backbone of radiopharmaceutical preparations includes radiochemists and in others, the educational background is even more
variable. Taking this into account, the EANM with its Radiopharmacy Committee has initiated a post-graduate education program in different universities throughout Europe (Germany, Switzerland, France, Slovenia and Italy) with a defined syllabus covering all specific aspects required in the small-scale preparation of radiopharmaceuticals (16). Together with two years of professional experience in radiopharmacy, candidates can apply for a certificate, thereby being recognized by the EANM as a QP in the small-scale preparation of radiopharmaceuticals.

It is the intention that this certificate will be accepted by respective authorities in Europe as a requirement for holding responsibility for the small-scale preparation of radiopharmaceuticals.

**Technological advances**

A high expertise in the field is also of importance due to the rapid technological advances in the field of radiopharmaceutical preparations. Whereas classical \(^{99m}\)Tc-radiopharmaceuticals are prepared manually despite some efforts towards automation (e.g. (17)), due to the high activities handled and specific radiation properties, the preparation of PET and therapeutic radiopharmaceuticals demands the use of non-manual approaches for radiation protection. Systems for radiopharmaceutical preparation may be semi-automated, whereby the operator still has to interfere in the process; the development, however, clearly follows the direction of full automation using a computer-controlled synthesis apparatus. They usually include the chemical synthesis of the radioactive compound, as it is shown in Fig.1 for the synthesis of \(^{18}\)F-2-fluorodeoxyglucose (FDG), automated purification procedures via solid phase extraction or HPLC and finally pharmaceutical formulation including sterile filtration.

The use of fully automated synthesis modules not only provides advantages in terms of radiation protection, but also improves standardization of procedures including fully automated documentation of all processes involved in the synthesis of radiopharmaceuticals. This makes compliance with GMP regulations easier. Furthermore, the limited intervention of the operator reduces operational errors and the risk of bacterial contamination of the product. In particular, the implementation of closed procedures for the whole process reduces risks of sterile operations to a minimum. This has even been taken into account by regulators, e.g. by allowing relaxations of clean room requirements when closed, automated systems are used.

![Figure 1: Synthesis of 2-[18F]fluor-2-deoxy-D-glucose via nucleophilic substitution.](image)

![Figure 1: Automated synthesis module for preparation of 18F-2-fluorodeoxyglucose (FDG) based on microfluidic technology using microliter amounts of solvents and applying ultra-short synthesis times, resulting in a total synthesis time of 7 min with a radiochemical yield of 81%.](image)
A recent trend in the development of automation of radiopharmaceutical preparation is the miniaturization of the processes. The introduction of microfluidics offers the possibility to concentrate whole radiopharmaceutical synthesis processes even on small chips. In a recent science paper (18), the synthesis of $^{18}$F-FDG using a chip-based synthesis module not bigger than a coin has been described. Figure 2 shows an automated small synthesis module for the preparation of $^{18}$F-radiopharmaceuticals based on microfluidic principles requiring microliter amounts of solvents and reagents. This technological advance is rapidly taken forward by small, highly specialized companies, and further developments can be expected every year. It can be foreseen that it will soon be technically possible to prepare short-lived radiopharmaceuticals on a small scale within a few minutes, even individually for one patient. It will be challenging for regulators to react to these rapid technological developments, and it will be interesting to see whether pharmaceutical legislation will adapt to microfluidic-based processes, allowing higher flexibility in radiopharmaceutical preparation towards individual patient needs.

CONCLUSION

The current practice of radiopharmaceutical preparation in Europe shows a great variety throughout the continent. This variety is a result of the historical development of the field in individual countries and of their different regulatory backgrounds. With the increasing importance especially of PET, but also of therapeutic applications introducing radionuclides with ultra-short half-life into the clinic and the general interest in individualized medicine, we currently see a trend towards unified regulations and a slow change in practice in most European countries. This process is currently ongoing and the radiopharmaceutical community, represented by the Radiopharmacy Committee of EANM, is giving increasing emphasis on convincing authorities with regard to the specific case of radiopharmaceuticals and the challenges in an ever-demanding regulatory environment in Europe.

REFERENCES


