6 Regulation of PET Radiopharmaceuticals Production in Europe

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Abstract

Radiopharmaceuticals are a unique species of pharmaceuticals, containing both a drug and a radionuclide. This distinctive character can be challenging from a regulatory point of view as both pharmaceutical good manufacturing practice (GMP) and radiation safety aspects have to be balanced against each other. As a consequence of this, the production of PET radiopharmaceuticals must comply with both GMP and local radiation safety rules. This chapter describes some of the regulatory framework that covers the human use of PET radiopharmaceuticals in Europe. For preclinical applications there are no regulations on production, apart from the local/national animal rights rules. The different approaches which may be used to obtain permission to use the PET radiopharmaceutical in humans are described. For "first in human" use in a clinical trial, the content of the Investigational Medicinal Product Dossier is described, also

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an approach to minimise the very costly toxicological studies. The essentials of GMP and quality management systems are explained. The chapter ends with some future directions and convenient GMP approaches.

6.1 Introduction

Radiopharmaceuticals are a unique species of pharmaceuticals, containing both a drug and a radionuclide. This distinctive character can be challenging from a regulatory point of view as both pharmaceutical good manufacturing practice (GMP) and radiation safety aspects have to be balanced against each other. As a consequence of this, the production of PET radiopharmaceuticals must comply with both GMP and local radiation safety rules. This chapter describes some of the regulatory framework that covers the human use of PET radiopharmaceuticals in Europe. For preclinical applications there are no regulations on production, apart from the local/national animal rights rules. This chapter starts with a brief history of GMP and pharmaceutical regulations and some of the regulatory organisations involved. The different approaches which may be used to obtain permission to use the PET radiopharmaceutical in humans are described. For "first in human" use in a clinical trial (CT), the content of the Investigational Medicinal Product Dossier (IMPD) is explained with respect to content, procedures and writing, also an approach to minimise the very costly toxicological studies. Next, the essentials of GMP and quality management systems (QMS) are explained. The chapter ends with some future directions and convenient GMP approaches.

6.1.1 Development of Pharmaceutical Regulations

The first pharmaceutical regulations in Europe were published in 1965 in response to thalidomide and other drugs which produced unexpected effects with tragic results [1]. However, it was more than 20 years before radiopharmaceuticals were considered as drugs [2–4]. Since then, regulations have become increasingly strict, as has their enforcement, though there are variations between countries [5]. Regulatory compliance now constitutes as significant proportion of the work in a centre which produces PET radiopharmaceuticals for clinical use. In addition to pharmaceutical regulations, which are addressed here, there is a range of other regulations, some of which conflict, which must be addressed. These include radiation protection of workers, patients and the public, radioactive waste handling and transport of radioactive materials. All in all, radiopharmacy is arguably the most highly regulated health profession. Managing this complexity is of utmost importance when planning and designing a PET radiopharmacy. Both GMP and radiation protection must be considered at all stages. If possible, meeting with both the medicines and radiation protection authorities in the early planning phase is highly recommended in order to achieve an efficient and compliant PET radiopharmacy. Environmental monitoring and control systems, such as air handling and other ancillary components, must be designed for heat dissipation, adequate humidity and temperature control, air quality and filtration systems, maintenance of room classes and provision of gas lines.

In many countries, PET radiopharmaceuticals are covered in the monographs of pharmacopoeias. A pharmacopoeia is a book containing directions and information on the identification and properties of drugs. A monograph is detailed information on purity criteria and tests to be used for a particular drug. If there is no national or regional pharmacopoeia available, the World Health Organization's International Pharmacopoeia (http://apps.who.int/phint/en/p/about/) may be used. Quality control of PET tracers is discussed in Chap. 5.

6.1.2 Regulatory Agencies

The practice of pharmacy and manufacturing of radiopharmaceuticals is regulated at a national level, with each country having a regulatory body

or "competent authority". In 1995 the European Union (EU) set up the European Medicines Agency (EMEA, later EMA; www.ema.europa.eu) to provide a framework for a single approval which would apply throughout the EU. However, submission of all products to the EMA was not compulsory, except for certain classes of pharmaceuticals, and national approvals are still possible [6]. The advantage of EMA route (*centralised procedure*) is a single approval which applies throughout the EU. However, the disadvantages include higher application fees, the cost of providing product information and labelling in all EU languages and the lack of a sufficient market in all nations. Only a small number of radiopharmaceuticals have EMA approval, but that number will continue to increase as central approval is the only route for therapeutic radiopharmaceuticals. At the time of writing, the only PET radiopharmaceuticals with EMA approval are the three amyloid imaging agents: florbetapir (Amyvid), florbetaben (NeuroCeq) and flutemetamol (Vizamyl). With its commitment to transparency, the EMA publishes detailed assessment reports, with only commercially sensitive material withheld. It may seem strange that the most widely used PET tracer, ^{18}F-fluorodeoxyglucose (FDG), is not approved by the EMA; however, it is a generic drug with local or regional production and there are no pan-European manufacturers.

Submission to individual countries is still possible, and most products which were licensed before the EMA was established are still regulated nationally. Once a product is accepted in one country, there is a *mutual recognition procedure* via which a product can be approved in another country without full separate evaluation. A third route is the *decentralised procedure* under which the product is submitted for approval in several countries at the same time with one country named as the reference country which carries out the full evaluation; this is a cheaper alternative to EMA approval.

It is only in recent years that the manufacture of PET radiopharmaceuticals began to be highly regulated and there are still differences between countries [7]. Some countries require all manufacturing of widely used tracers such as FDG to be performed under a licence, albeit with an abridged application as described in Sect. 6.2.1. The United Kingdom is unique in having a "specials" licence under which a wide range of products that are not commercially viable can be manufactured. It has the additional advantages that products do not need to be released by a qualified person (see Sect. 6.1.6) and prior approval of new products is not required.

Pharmaceutical regulations were intended for the pharmaceutical industry and commercial scale manufacturing. Full compliance with GMP is difficult in small facilities producing short-lived radiotracers because of the small number of personnel, half-life constraints on analysis and rapid reuse of shared equipment (see Sect. 5.2). The first official recognition of the special status of radiopharmaceuticals came in the EU Clinical Trials Regulations of 2014, wherein it was acknowledged the clinical trials of diagnostic radiopharmaceuticals did not fall within the regulations [8, 9]. This opens the door to the use of risk assessment as a tool for interpretation of legislation [7].

6.1.3 Pharmaceutical Inspection Cooperation Scheme (PIC/S)

Although inspections of pharmaceutical manufacturing facilities are carried out by the national authorities, the Pharmaceutical Inspection Convention has a cooperation scheme, PIC/S, under which there is a degree of harmonisation of inspection standards throughout Europe (www.picscheme.org). Of most relevance is the guide to good practices for the preparation of medicinal products in healthcare establishments, which now has an annex on radiopharmaceuticals [10]. Although PIC/S aims to harmonise inspection standards, each national authority retains full responsibility.

6.1.4 The European Pharmacopoeia (*Ph. Eur*)

Although most countries have their own pharmacopoeia, there is also a European Pharmacopoeia

(http://online.edqm.eu/EN/entry.htm) which has legal status in all nations. It contains general monographs on classes of drugs such as radiopharmaceuticals or parenteral preparations as well as methods of analysis. Recently a general chapter on extemporaneous preparation of radiopharmaceutical preparations has been added.

Monographs on individual radiopharmaceuticals, at the time of writing approximately 70, specify such aspects as chemical and radionuclidic identity, tests for parameters such as pH, radionuclidic impurities and chemical and radiochemical impurities as well as setting limits for each. Importantly, the specifications are for the end product and do not dictate the route of synthesis except for its impact on the impurity profile. The remit of the *Ph. Eur* is drug quality; inclusion in the pharmacopoeia is independent of licensing status or clinical utility.

Radiopharmaceutical monographs are written ("elaborated") by Group 14, composed of academic, commercial and regulatory specialists. Once a monograph has been drafted, it is circulated for comment by national authorities, professional bodies and other concerned parties before final revision and acceptance.

Increasingly the *Ph. Eur* is being seen as the route forward for introduction of new compounds. The short half-lives of PET radiopharmaceuticals limit their market to local distribution; thus only extremely high-volume products will be manufactured commercially. However, once a radiopharmaceutical has a *Ph. Eur* monograph, it can be prepared locally to accepted quality standards under the magistral approach described in Sect. 6.2.3. The tests in the monographs are usually (1) identification, by gamma-ray spectrometry, half-life or high-pressure liquid chromatography (HPLC); (2) pH determination; (3) radionuclidic purity, by gamma-ray spectrometry or half-life; (4) chemical purity, by HPLC; (5) radiochemical purity, by HPLC with a radioactivity detector or by TLC and radioactivity scanner; (6) residual solvents, by gas chromatography; (7) sterility; (8) bacterial endotoxins; and (9) radioactivity, by measurement in an ionisation chamber ("dose calibrator"). See Chap. 5.

6.1.5 International Conference on Harmonisation (ICH)

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. It was established in 1990 and has gradually evolved to respond to the increasingly global face of drug development, so that the benefits of international harmonisation for better global health can be realised worldwide. The mission of ICH is to achieve greater harmonisation to ensure that safe, effective and high-quality medicines are developed and registered in the most resource-efficient manner (http://www.ich.org/home.html).

6.1.6 Qualified Person (QP)

The EU pharmaceutical directive of 2001 [5] designates the status of *qualified person* (*QP*) who is authorised to release products for clinical use under a manufacturing licence or clinical trial licence. To be eligible to be a QP, the individual must be a registered pharmacist, chemist or biologist who has sufficient experience in a manufacturing environment and who has passed an exam conducted jointly by the professional registration body and the national authority.

6.2 Regulatory Framework

There are three main routes to get a radiopharmaceutical into the clinic for human use: (1) marketing authorisation, (2) clinical trial and (3) the "magistral approach".

A marketing authorisation is very expensive ($$$$$) and takes years to obtain. A clinical trial is less expensive ($$$) and takes at least a year. In contrast, the "magistral approach" is the least expensive ($) and can take only a matter of months. A marketing authorisation may be used for both established and new tracers. A clinical trial is mainly for novel tracers ("first in human"

studies) and for new or additional uses of an already established tracer. The magistral approach is for known radiopharmaceuticals that have been previously tested in man, and preclinical data, such as safety, efficacy, toxicology and dosimetry, is available.

6.2.1 Manufacturing Authorisation (MA)

A manufacturing authorisation may be issued by the EMA or by a national authority. The documentation which must be submitted is extensive, as described in Sect. 6.3.2. If it is a novel tracer, the evidence of efficacy and safety will have been obtained from a clinical trial, as described in Sect. 6.2.2.

Because of the cost of obtaining an MA, this route will only be taken if there is a commercial market for a tracer or if a national authority requires an MA even for local use. This mainly applies to widely used tracers such as FDG.

For generic tracers (i.e. no longer under patent) with well-established use, an abridged application may be submitted where literature references are used for the non-clinical and clinical data. This applies if the tracer has been in use for 8–10 years [article 10 of reference 5]. The manufacturer only needs to present data on product quality. This is discussed in Sect. 6.3.2.

6.2.2 Clinical Trial

Volume 10 of Eudralex contains all the information needed for clinical trials [11]. Trials are conducted under the guidelines of the International Conference on Harmonisation (ICH) of pharmaceutical trials [12]. The quality data to be submitted is similar to that required for a manufacturing authorisation.

In addition to the quality and safety of the product, trials must be performed according to good clinical practice (GCP) which ensures the quality of the data obtained from the trial and safeguards the human subjects who take part in trials. This too is enshrined in Eudralex [11]. In addition to the inspections of manufacturing facilities, there are also GCP inspections which assess the systems and data kept at clinical research sites. It is required that every employee who is involved in a clinical trial receives GCP training with updates at 2–3 year intervals. Thus, radiochemists who provide data which will be part of the clinical trial must undergo this training.

6.2.3 Magistral Approach/ Extemporaneous Preparation

A less formal system is the magistral approach. A *magistral formula* is a pharmaceutical compound prepared by the pharmacist or someone under his/her direction for a given patient according to a prescription and following the technical and scientific standards of the pharmaceutical art. An *official preparation* is a pharmaceutical compound developed or prepared by a pharmacist or someone under his/her direction which is listed and described by the national formulary. The two ancient terms provide a means for the small-scale production of PET tracers essentially under the practice of pharmacy rather than a manufacturing authorisation. In the United Kingdom, this is termed a Sect. 10 exemption from the Medicines Act.

6.2.4 Documentation

The general requirements for the approval of tracers include process validation, product quality (chemical purity, radiochemical purity, stability, sterility, bacterial endotoxins, bioburden) and analytical method validation according to ICH guidelines (specificity, repeatability, precision, sensitivity, linearity, accuracy) [13].

There must be a written application which includes description and composition of the drug product, description of the manufacturing process and process controls, control of reagents and excipients (including the quality and purity of precursor) and control of drug product (specifications, analytical methods, stability).

The formats for manufacturing authorisation and clinical trial are identical, with the exception

on the numbering. It may be advisable to use the same format for the magistral approach as the assessors are familiar with it. Use all the points in the template and write "not applicable" or "N/A" in the fields where it is so.

6.3 Drug Development and Approval

6.3.1 Stages of Drug Development

The process of drug development can be broadly divided into two stages: preclinical and clinical. Each of these can then be subdivided into multiple parts.

6.3.1.1 Preclinical Studies

The preclinical development of a drug begins with chemistry, whether a novel compound or a variant on a known synthetic or natural compound. With radiopharmaceuticals there is the added problem of where to put the radioactive atom on the molecule. Among the factors in this choice is ease of chemistry to perform the radiolabelling in high yield, generally as the final step of synthesis to avoid losses due to radioactive decay during subsequent synthetic steps. The location of the label should not significantly change the biological properties of the molecule, particularly if it is designed to mimic a natural substance and bind to a receptor. Furthermore, the label should be metabolically stable so as not to complicate image interpretation or mathematical modelling.

Once the chemistry has been established, though not necessarily optimised, the chemical and in vitro biological properties of the labelled molecule can be established. These include stability in a biological milieu, such as incubation with human serum at 37 °C. There may be in vitro binding assays which can be performed to characterise the binding affinity and selectivity of the compound.

If a potential radiotracer shows appropriate in vitro properties, it can be evaluated in small animals, generally mice or rats. Increasingly, transgenic species are being used in which human tumours can be grown or human diseases mimicked. In recent years, preclinical PET/CT and SPECT/CT scanners have become widely available which provide excellent spatial resolution (~1 mm) and allow longitudinal studies in the same animal, which is particularly important with expensive transgenic rodents [14, 15]. With only a small number of animals, it can be established whether the radiotracer does indeed target the desired lesion and whether uptake in adjacent organs interferes with visualisation of the target. These studies also give an idea of the route (s) of excretion of the radiotracer. In the past, imaging studies were only semi-quantitative, but quantitative values can be obtained by tissue biodistribution studies following sacrifice of the animal. Individual organs are dissected, placed in preweighed counting tubes, weighed and assayed in a gamma well counter along with a known dilution of the dose. This allows determination of the % dose per organ and % dose per gramme of each organ and calculation of target to background ratios. With current preclinical PET/CT and SPECT/CT systems, absolute quantification can be performed on imaging studies alone. Displacement studies can be performed with a nonradioactive drug which competes with the radiotracer for binding to the same target site. These animal studies allow prediction of human radiation dosimetry of the radiotracer. See Chaps. 3 and 14 for further details on PET dosimetry and PET kinetic modelling, respectively.

6.3.1.2 Toxicological Studies

There is also a need for preclinical safety, toxicology and dosimetry data. The toxicology is generally the most expensive part of the preclinical data. Normally for radiopharmaceuticals, biodistribution and dosimetry data from preclinical studies is often available, including imaging, autoradiography and direct measurement of radioactivity in harvested tissues and organs. Such studies may give detailed quantitative data on accumulation and elimination in tissues and excretion pathways. Using this data the design of extended single-dose toxicity studies may be focused on high-risk organs and tissues, thereby reducing the requirement for histopathological

data in all organs, but focusing on main organs where the radiopharmaceutical accumulates.

If amounts are minute (in the microgram range), the Threshold of Toxicological Concern (TTC) approach may be used. Medicinal products such as radiopharmaceuticals may be exempt from toxicological studies when (single) doses up to 120 μg are used [16]. The ICH has also recently adopted the TTC approach in the assessment of DNA reactive mutagenic impurities in pharmaceuticals [17]. For larger molecules, such as peptides and monoclonal antibodies, one can argue that the molar amount is of importance. The adopted/assumed molecular weight for the medicinal product is set to 300 g/mol. For larger molecules such as proteins, FDA guidance sets the limit to <30 nanomoles. "Due to differences in molecular weights as compared to synthetic drugs, the maximum dose for protein products is ≤30 nanomoles" [18]. This corresponds to <100 μg of a drug having a molecular weight of 300.

6.3.1.3 Clinical Studies

If the chemical, in vitro and small animal studies are promising, the decision can be taken to evaluate the potential radiotracer in humans. In the past this was quite informal, with the initial volunteers often being the researchers themselves or graduate students in their departments. However, now this is highly regulated [19–21].

Traditionally, clinical studies of drugs proceed through Phase I, Phase II and Phase III before regulatory approval. However, with radiopharmaceuticals an initial step called Phase 0, pre-Phase I, microdosing (Europe) or exploratory Investigational New Drug (IND, USA) is often employed. Microdosing is defined as the administration of no more than 100 micrograms of the tracer and no more than 1/100 of the dose producing a pharmacological effect, which is often achievable with radiopharmaceuticals, particularly with PET agents [22, 23]. The toxicity testing for microdosing studies is much less rigorous than for later studies. Only an extended single-dose acute toxicity study in one species, generally a rodent, is required, with sacrifice of animals after 1 and 14 days followed by necroscopy. A microdosing study in 5–10 subjects will give a good indication of whether the radiotracer shows the same properties in humans that it did in animals and informs the decision on whether to proceed with product development.

A new potential radiopharmaceutical is classed as an investigational medicinal product (IMP). One of the documents required in support of a clinical study is an IMP Dossier (IMPD) which describes how the radiotracer will be produced and tested and summarises the information available about the compound. The Radiopharmacy Committee of the European Association of Nuclear Medicine has published guidance on the preparation of IMPDs for radiopharmaceuticals [24]. An important part of the IMPD is the criteria for release of a product for clinical use. The dossier addresses such aspects as radiochemical purity, pH, specific activity and content of residual solvents, as well as sterility and apyrogenicity.

There must also be an Investigator's Brochure (IB) which contains some of the same information but has a more clinical viewpoint.

Phase I studies are generally carried out in small numbers (<10) of normal volunteers, though with oncology tracers, sometimes patients are used. The main aim of Phase I is safety, though with the small chemical quantities of radiotracers, this is rarely a real concern. Usually whole-body images are obtained at different time points to allow calculation of radiation dosimetry in humans.

Phase II studies are proof of principle to demonstrate targeting of the intended organ or disease process. With radiotracers, Phase II is also used to determine the optimal imaging protocol which will be used in subsequent studies.

Phase III studies are the definitive efficacy studies required for receipt of a marketing authorisation. With radiopharmaceuticals the number of patients required is much smaller than for therapeutic drugs. However, the regulatory authorities prefer to see two independent Phase III studies. It may be necessary to perform multicentre studies in order to accrue a sufficient number of patients. Each phase must be approved by the medicines agency before the next is undertaken.

6.3.2 Data Needed for Submission

The clinical trial application to a national authority or to the EMA consists of several sections [25]:

1. Module I contains administrative information relevant to the authority to which the application is being made. The remainder of the application is called the Common Technical Document (CTD) and consists of modules II through V. The CTD was introduced by ICH in 2003 and standardises the presentation of data to regulatory authorities.
2. Module II contains summaries of quality data, preclinical studies and clinical studies, while modules III through V contain the details of those three aspects. The quality data includes the chemistry, manufacturing and controls (CMC), in the same format as was presented in the IMPD. The preclinical section includes toxicity studies which must be performed to Good Laboratory Practice (GLP) standards.

The structure of the CTD is shown in Fig. 6.1. For generic or well-established tracers, an abridged application may be submitted [article 10 of reference 5]. The red circle in Fig. 6.1 indicates which sections are included in the abridged application. The non-clinical and clinical trial data normally required for an application may be replaced by appropriate scientific literature. This kind of application is also known as a bibliographic application.

Many radiopharmaceuticals are manufactured directly to the final drug product; i.e. the drug substance or active pharmaceutical ingredient (API) is not isolated before formulation. This has some consequences for the CTD. Section "6.3.2. P Drug Product (Name, Dosage Form)" will be essentially the same as Sect. "6.3.2. S Drug

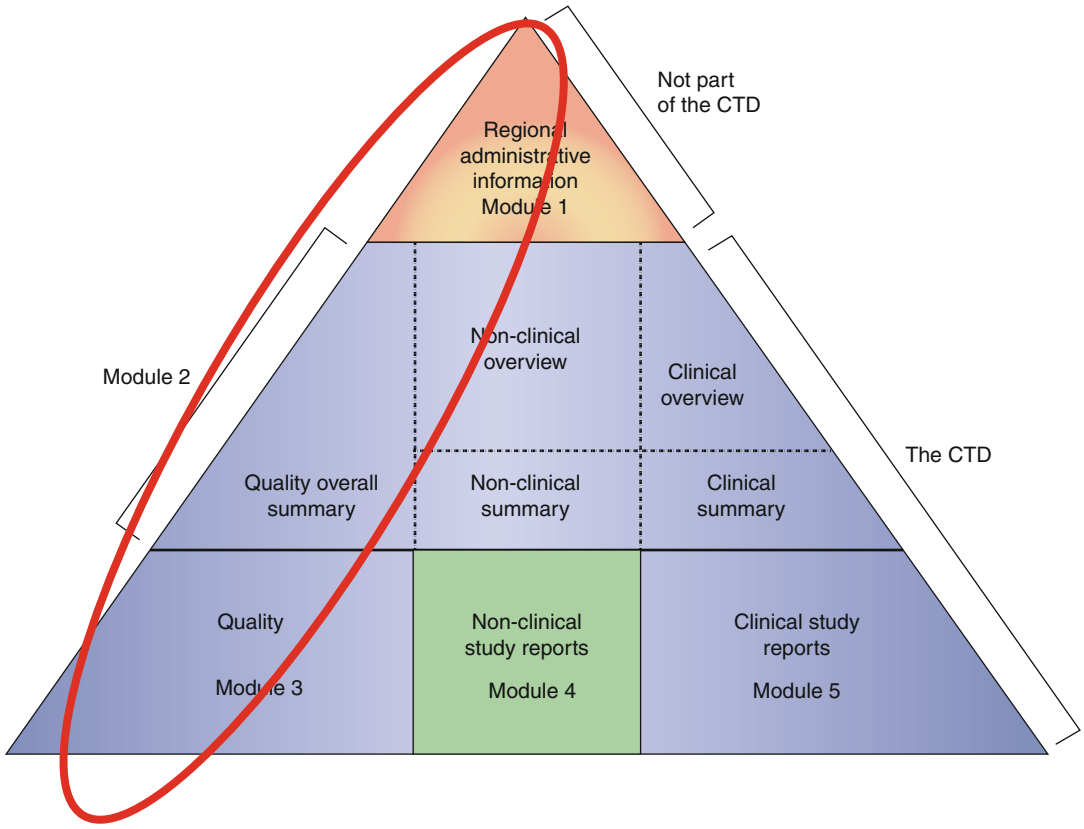

Fig. 6.1 The structure of the Common Technical Document (*CTD*) pyramid. *Module 1* is region specific and *modules 2*, *3*, *4* and *5* are intended to be common for all regions. The topics within the *red circle* are the components of the abridged application (From http://www.ich.org/products/ctd.html)

Substance (Name, Manufacturer)" [24]. Copy and paste these sections; do not use different wording as this may confuse the assessor at the regulatory body. There will more about the language for applications in "scientific writing" section.

For each marketed product, there must be a Summary of Product Characteristics (SPC or SmPC) which presents information about the product, including dosimetry and instructions for its use. The EMA is developing standard SPCs for generic products [26].

6.4 Scientific Writing

> My words fly up, my thoughts remain below; Words without thoughts never to heaven go (Claudius in Shakespeare's "Hamlet", Act III, scene iii).

Any application submitted to a regulatory body or competent authority must be very stringent and sober in both structure and language. It is, unquestionably, not a scientific paper to pass a peer review, but a description of drug manufacturing and quality control. Not all assessors are experts on radiopharmaceuticals and will thus react to any ambiguous or unclear wording.

Example: How Not to Write

Radionuclidic impurities

Radioactive oxygen-14 and nitrogen-13 may form as a result of minor side reactions in the cyclotron target: $^{14}N(p,n)^{14}O$ and $^{16}O(p,\alpha)^{13}N$. N-13 and O-14 are both positron-emitting radionuclides. The presence of O-14 in the drug substance may be ruled out as a significant contaminant because it has an ultrashort half-life of O-14 ($T_{1/2} = 70.6$ s); thus in the course of synthesis ca 25 min, it will decay to 4.7×10^{-7} of its original amount. N-13 can appear in the form of gaseous ^{13}N-labelled oxides (e.g. [^{13}N]NO, [^{13}N]NO_2, etc.). The presence of ^{13}N would alter the measured half-life of the drug substance and would be seen as a radiochemical impurity during chromatographic analyses. This has not yet been observed. It is worth noting that ^{11}C in its process from starting material [^{11}C]CO_2 to the final product undergoes several chemical transformation steps with intermediate purifications. Therefore the probability for unwanted N-13 and O-14 species to survive through the same pathway as C-11 and end up in the final formulation is expected to be very low.

This is lengthy and confusing. Stating "not yet been observed" implies that it may be observed. Similarly, "the probability for unwanted" implies that there is a probability.

Example: How to Write

Radionuclidic impurities

Radioactive nitrogen-13 may form as a result of a minor side reaction in the cyclotron target: $^{16}O(p,\alpha)^{13}N$. N-13 can appear in the form of gaseous ^{13}N-labelled oxides (e.g. [^{13}N]NO, [^{13}N]NO_2, etc.). However, contamination of the final product with ^{13}N is not possible because the chemistry of nitrogen oxides is different from that of the starting material, [^{11}C]CO_2, which undergoes multiple chemical transformation steps with intermediate purifications.

This is short and sweet. By saying "is not possible", there is no doubt that it cannot be present. The language should be concise and formal, not verbose and/or sounding like a scientific investigation.

Example: "The product is purified by means of XXX and no impurities have been found" rather than "The product is purified by means of XXX, the possible impurity YYY which can potentially be produced by…..has so far not been detected".

Example: "All batches passed the sterility test", not "All batches passed the sterility test. However…"

Example: "The product is thus safe for human use", not "The product is thus safe for human use, yet some investigations have found…"

Have enough data/information to make a clear statement. It is better to spend a few hours extra in the laboratory than spending a few months in discussions with the competent authority.

6.5 Good Manufacturing Practice (GMP)

6.5.1 Components of GMP

The goal of pharmaceutical GMP is to ensure a consistent high-quality product which is appropriate for its intended use and which meets the specifications of its marketing authorisation. Because standards are constantly changing, the term current good manufacturing practice, cGMP, is often used. The three main components of GMP are facilities and equipment, personnel and procedures and documentation, all carried out within a quality management system. European rules for GMP are described in Eudralex volume 4 [27] with specific reference to radiopharmaceuticals in annex 3 [28] and investigational medicinal products in annex 13 [29].

6.5.1.1 Facilities and Equipment

The design and construction of facilities must afford a clean environment. Surfaces must be impervious and able to withstand regular cleaning. Activities must be segregated with interlocking doors to prevent cross-contamination. There must be a cascade of filtered air pressure from the cleanest area to the exterior to minimise the ingress of particles. This is achieved by heating, ventilation and air conditioning system (HVAC) with high-efficiency particulate air (HEPA) filters. Similarly, there must be a regimen of gowning up to prevent staff from carrying contaminants into the clean areas. Materials are sanitised and then transferred in via hatches with interlocking doors. Aseptic processes must be carried out within an appropriate environment of filtered air. Generally, radiosynthesis can be carried out in Grade C, but sterile filtration and dispensing must be carried out in Grade A. These are generally achieved with a hot cell, pharmaceutical isolator or laminar airflow cabinet. All equipment must be kept in good working order with regular checks of performance and records of maintenance undertaken. Proper operation of the facility must be documented by routine environmental and microbiological monitoring. This includes a combination of measurements of air flows and air change rates, active air sampling and particle counting and routine microbiological monitoring including agar settle plates, contact plates and finger dab plates. All of this is covered by the site master file (SMF).

6.5.1.2 Personnel

Personnel must be adequately trained in any procedures they carry out, with a training record. The training record must indicate that the member of staff has read the SOP and has demonstrated competence with evidence of a certain number of monitored activities. The responsibilities and authorities of each grade of staff must be specified. Persons who perform aseptic procedures must undergo periodic revalidation of their competence. If production facilities are shared with a research institution, the research personnel must be adequately trained in GMP regulations, and the quality controller (see below) must review and approve the research activities to ensure that they do not pose any hazard to the manufacturing of radiopharmaceuticals.

There must be a person designated as production manager, sometimes called responsible person. This person is responsible for the routine operation of the facility to ensure that the radiopharmaceuticals are produced to GMP standards. This includes ensuring that there are sufficient numbers of suitably trained staff available on a daily basis. This person makes sure that all documentation is complete before products are passed on to the quality assurance department.

There must be another independent person designated as quality controller. This person takes ultimate responsibility for the quality of the radiopharmaceuticals produced, though the act of release may be delegated to a suitable trained person. In some situations the quality controller might also be a qualified person.

6.5.1.3 Procedures and Documentation

All Standard Operating Procedures (SOPs) must be written down, approved and reviewed at regular intervals. There must be contemporaneous manufacturing records which document the adherence to SOPs and record the identities and quantities of all materials used and any in-process checks, all of which must be initialled or signed

by the operator and checker. Quality assurance results must include evidence that the analytical equipment had been properly calibrated. There must be a Validation Master Plan (VMP).

One of the underpinning features of GMP is the quality of starting materials. Precursors must be obtained from approved vendors. There must be a process for auditing or inspecting vendors. It may be possible for a single such audit to be performed on behalf of a number of PET centres in the same country. All chemicals which remain in the final formulation must be obtained from certified pharmaceutical suppliers. In particular, active pharmaceutical ingredients (API) must be obtained from a certified GMP source.

6.5.1.4 Quality Management System (QMS)

In recent years, inspectors have placed increasing emphasis on the quality management system [30]. Indeed, this chapter was revised in 2013. Quality management is a wide-ranging concept, encompassing all matters which individually or collectively influence the quality of a product. The components of a QMS include the following. Product and process knowledge is managed throughout all life cycle stages. Managerial responsibilities are clearly specified. Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and verifying that each delivery is from the approved supply chain. Processes are in place to assure the management of outsourced activities. The results of product and process monitoring are taken into account in batch release, in the investigation of deviations and with a view of taking preventive action to avoid potential deviations occurring in the future. All necessary controls on intermediate products and any other in-process controls and validations are carried out. Where the true root cause (s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause (s) and to addressing those in order to assess which might be responsible. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system-based errors or problems have not been overlooked. Appropriate corrective actions and/or preventative actions (CAPAs) should be identified and taken in response to investigations in a timely manner. The effectiveness of such actions should be monitored and assessed, in line with quality risk management principles. There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the pharmaceutical QMS.

6.5.2 Challenges for PET

There are two separate challenges for the application of GMP to the manufacture of PET radiopharmaceuticals. The first is dictated by the short half-lives of most radionuclides used in PET, e.g. ^{18}F, 109 min; ^{11}C, 20 min; ^{13}N, 10 min; and ^{15}O, 2 min. There is no time for all quality parameters to be assessed before release for clinical use. Following risk assessment it must be specified which parameters can be determined retrospectively. This would include sterility testing and determination of levels of residual solvents. If at all possible, endotoxin testing, as a surrogate of sterility testing, should be performed before release, while sterility testing is performed post release. Endotoxins are heat-stable toxins released from the cell wall of gram-negative bacteria; thus, the absence of endotoxins suggests that the product does not contain bacteria. Before a new product is introduced, there must be a number of validation runs with full analysis to establish the quality of the product and its reproducibility.

The second challenge is the small-scale production, usually only a few doses at a time, in relation to the number of members of staff who would be required for implementation of full GMP. There should be segregation of responsibilities for production and quality control, and there should be independent release. Moreover, this small-scale production of a range of products is carried out with a small number of automated synthesis units. In the past this often involved reusable apparatus for which there had to be a validated cleaning procedure between operations and a strict regime of segregation.

Nowadays sterile single-use cassettes are available for many products, making production more reliable and less risky [31]. The Radiopharmacy Committee of the European Association of Nuclear Medicine has published guidance on good radiopharmacy practice (cGRPP) for the preparation of radiopharmaceuticals on a small scale [32].

6.6 Future Directions

6.6.1 New European Clinical Trials Regulations

The implementation of the European Clinical Trials Directive of 2001 had the unintended effect of reducing the number of clinical trials carried out in Europe [33]. Following consultation, the Directive was amended and reintroduced as a regulation [8]. Even though this regulation entered into force on 16 June 2014, it will apply no earlier than 28 May 2016. As a result of lobbying during the revision process, the special status of radiopharmaceuticals has been recognised, and there has been a relaxation of several requirements for radiopharmaceuticals [9].

Article 61, paragraph 5, states that the requirement for an investigational medicinal product (IMP) manufacture authorisation will *not* apply to "preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State". There are two important points within this statement. Firstly, it only applies to diagnostic radiopharmaceuticals, not therapeutic. Secondly, it only applies to small-scale preparation in hospitals and affiliated centres but does allow for supply to other centres taking part in the same clinical trial but lacking facilities for preparation of radiopharmaceuticals.

It is further stated in article 63, paragraph 2, the full requirements of GMP will not be applied to preparation of radiopharmaceuticals under this exemption. This will reduce the regulatory burden on PET centres but will not compromise the quality of the radiopharmaceuticals produced.

Finally, article 68 simplifies the labelling requirements for containers used to hold radiopharmaceuticals, recognising that it is a challenge to fit all the components required for an IMP product label onto a small square of adhesive paper.

It is anticipated that this precedent may be built upon in future revisions of European pharmaceutical legislation which affects PET radiopharmaceuticals.

6.6.2 Recognition of Special Status of Radiopharmaceuticals

Following on from the recognition of radiopharmaceuticals in the Clinical Trials Regulation [8], the relatively new PIC/S guidance document with annex 3 on radiopharmaceuticals contains some useful tips and ideas for the non-commercial "in-house" manufacturing of radiopharmaceuticals [10]. In this document, for example, the use of risk assessment can justify less stringent requirements for the environment that is written in annex 1 of Eudralex [27].

There can be a conflict in the requirements of GMP and radiation protection regulations as the former consider only the patient's safety and the latter only the worker's safety. In a case where the two regulations cannot be met, a decision based on a risk assessment should be made in order to determine which is of higher impact. Weighting should be applied based on the

probability, risk and danger for the employees versus the patients, e.g. number of employees exposed to risk × probability of an incident × impact of incident to be compared with number of patients exposed to risk × probability of an incident × impact of incident.

An example of the use of risk assessment is the GMP requirement for an integrity test of the sterile filter after use: the filter contains residual radioactivity and thus poses a radiation risk. If many filters (>10) have been tested and the product has been demonstrated to be sterile each time or if the sterile filter is removed and the product is tested for bioburden (the microbial/bacterial load before sterile filtration) and is low (<1 CFU/10 mL; CFU – colony-forming unit) each time, one can make a risk assessment in order to avoid doing the sterile filter integrity test until the radioactivity has decayed.

6.6.3 Risk Assessment Approaches

As already mentioned in Sect. 6.6.2, risk assessment can be used to justify less stringent environment for the manufacturing of radiopharmaceuticals. Two of the most frequent approaches to risk assessment in the manufacturing of tracers are FMEA (failure modes and effects analysis) and FMECA (failure mode, effects and criticality analysis). Both approaches provide an evaluation of potential failure modes for processes and their likely effects. They investigate the probability of occurrence (O), degree of severity of the consequences (S), and the detectability (D). The occurrence, severity and detectability are placed in a matrix and then the Risk Priority Number (RPN) is calculated as O × S × D. RPN is a method to determine the criticality.

An example of a three-level FMEA/FMECA matrix:

Parameter	Level	Score	Description
Probability of occurrence (O)	Low	1	Very unlikely to occur
	Medium	2	Moderately likely to occur
	High	3	High probability of occurrence
Severity (S)	Low	1	Expected to have little or brief negative influence
	Medium	2	Expected to have a medium negative influence with possible minor long-term harm
	High	3	Expected to have a harmful or hazardous impact, including long-term effects with possible catastrophic or fatal effect
Detectability (D)	High	1	All failures are expected to be detected and the consequences avoided
	Medium	2	Some but not all failures are expected to be detected and the consequences avoided
	Low	3	None of the failures are expected to be detected and the consequences avoided

6.6.3.1 Risk Evaluation

(Sub) System	Function	Failure mode	Failure cause	Consequences	O	S	D	RPN	Action

Continue analysing the problem and fill out the schedule above and calculate RPN for each subsystem. Find suitable action levels depending on the character of the problem, for example:

RPN ≥12	High risk, unacceptable, action needed
5< RPN <12	Medium risk, further investigations to decide actions
RPN <5	Low risk, acceptable

Document the actions decided and their outcome.

Risk Control One way to control the risks is to create a risk matrix.

6.6.3.2 Risk Matrix

Probability (OxD)

Severity (S)	Low		Medium		High	
Low	1	2	3	4	6	9
Medium	2	4	6	8	12	18
High	3	6	9	12	18	27

Level 1 = Acceptable	Level 2 = ALARP (As Low As Reasonably Practical)	Level 3 = Intolerable

To construct this matrix, the probability and detectability parameters are multiplied together and tabulated against the severity parameter. Standard risk classification is used to discriminate between levels of risk.

The ALARP level will be determined according to the kind of problem being assessed. You will also have to consider regulatory requirements and other demands stated by authorities, for example, marketing authorisations. Further information can be found in the ICH Q9 guideline [34].

6.6.4 Quality by Design (QbD)

Quality by design can be seen as an approach similar to parametric release. All critical parameters and set points are evaluated, normally using multivariate analysis. Once this is done, the knowledge space and design space are assigned (see Fig. 6.2a). As long as the set points and parameters are within the design space (see Fig. 6.2b), the finished product will meet the specifications and may be released. This approach may demand more in-process controls but should demand less or less frequent, quality control, thus enabling easier and faster release of radiopharmaceuticals. Further information can be found in the ICH Q8(R2) guideline [35].

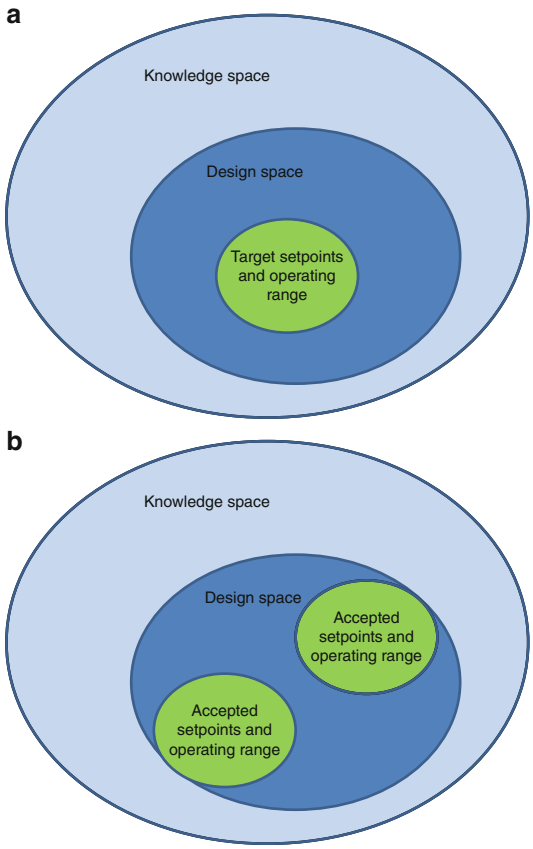

Fig. 6.2 (**a**) The QbD spaces. (**b**) Accepted set points and operating ranges within the QdB spaces

Conclusion

All in all, GMP is here to stay. It started as a reactive process to the inconsistencies in drugs and the manufacture thereof but is slowly and steadily changing towards being a proactive approach for the manufacturing of drugs. Globalisation pushes the different regions and countries to harmonise their regulations for medicinal products, and radiopharmaceuticals are becoming recognised as a special breed of drugs. In the near future, it may become easier to gain approval for the use of PET radiopharmaceuticals in humans as the special status of radiopharmaceuticals is recognised.

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