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Good Practice for Introducing Radiopharmaceuticals for Clinical Use

IAEA
International Atomic Energy Agency

GOOD PRACTICE FOR INTRODUCING RADIOPHARMACEUTICALS FOR CLINICAL USE

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GOOD PRACTICE FOR INTRODUCING RADIOPHARMACEUTICALS FOR CLINICAL USE

INTERNATIONAL ATOMIC ENERGY AGENCY
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FOREWORD

Nuclear medicine is one of the best examples of the peaceful application of atomic energy. Therefore, the IAEA promotes the development of nuclear medicine techniques in both imaging and therapeutic applications as part of the clinical management of certain types of disease. Nuclear medicine relies on the use of pharmaceuticals labelled with radioactive isotopes to study, diagnose and treat disease. One of the major strengths of this approach is the possibility of exploring different physiopathologic processes by means of different radiotracers. It is therefore evident that the introduction of new radiopharmaceuticals would greatly benefit the practice of nuclear medicine, which in turn would enhance the quality of successful health care and patient management.

However, there are several barriers to the introduction of new radiopharmaceuticals. In many countries, there is a lack of clarity and guidelines with respect to the rules and regulations governing the approval and registration of radiolabelled drugs. The objective of this publication is to review practices in different countries, to explain the necessary steps and to provide references for conducting human studies with new radiopharmaceuticals whose quality, safety and efficacy have already been established in other countries.

There is a clear need for the introduction of new radiopharmaceuticals into clinical use, which could exploit the limitations of currently established radiotracers and increase the number of radiopharmaceuticals available for physicians to the benefit of patients. The established use of a radiopharmaceutical in one country should facilitate its introduction into others. New radiotracers are of great benefit in the evaluation of cancer, as well as heart and brain diseases. There is also a rapidly growing interest in tracers that are aimed at diagnosing infectious and inflammatory diseases. The scope of the good practices described here is to provide practical support for the introduction of new radiotracers, ensuring at the same time, that a safe and high quality product is administered to the patient at all times. The aim is not to provide a detailed list of all the possibilities when introducing a new radiopharmaceutical into clinical practice. Instead, the good practices outline the necessary and important steps prior to introducing safe and reliable radiopharmaceuticals into clinical practice.

In countries with established experience in nuclear medicine, the most common route of supplying radiopharmaceuticals is through a network of commercial production sites. Here, the commercial producer oversees the processes of approval and marketing authorization. However, there may be an absence of commercial interest for some radiopharmaceuticals, owing to limited marketing opportunities. Moreover, there are several countries which are currently not covered by the radiopharmaceutical provider distribution network. Therefore, an additional objective of this publication is to provide a useful reference to facilitate and expedite the introduction of radiopharmaceuticals already in clinical use in other countries, with the aim of providing alternative diagnostic solutions for improved patient care.

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EDITORIAL NOTE

This publication has been prepared from the original material as submitted by the contributors and has not been edited by the editorial staff of the IAEA. The views expressed remain the responsibility of the contributors and do not necessarily represent the views of the IAEA or its Member States.

Only diagnostic radiopharmaceuticals were considered in the preparation of this publication. Indications for radioactive compounds with therapeutic effects were not considered. Guidance provided here, describing good practices, represents expert opinion but does not constitute recommendations made on the basis of a consensus of Member States. The good practices are not intended to provide an alternative interpretation of existing regulatory requirements for conducting human studies with radiopharmaceuticals. They are intended to provide an educational and practical tool for understanding the basic scientific principles and methods currently considered as the most effective to guarantee patient safety for the use of radiopharmaceuticals in medical practice. The good practices are not intended to support the processes of marketing application of any new radiopharmaceuticals of commercial interest.

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CONTENTS

1. INTRODUCTION

1.1. BACKGROUND

Radiopharmaceuticals are radiolabelled compounds designed to deliver diagnostic information as a result of their incorporation with selected cellular targets. These exquisite molecular tools are essential components of nuclear medicine technology and must be prepared prior to administration to the patient. The production of radiopharmaceuticals must be performed by a licensed commercial organization, or alternatively using in-house good manufacturing practice (GMP) compliant facilities.

According to the most widely accepted definition, a radiopharmaceutical is classified as a 'medicinal product' and, therefore, its production, characterization and quality control testing should comply with the rules for manufacturing/compounding sterile products intended for human injection. These rules have evolved over the years to ensure that a safe and high quality product is administered to the patient at all times.

In countries that are experienced in this technology, the most common route of supplying radiopharmaceuticals is through a network of commercial production sites. In this context, the commercial producer retains the responsibility of ensuring that the quality and safety of the radiopharmaceutical product complies with internationally accepted standards. However, in-house preparations are also permitted when performed in a GMP compliant facility.

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) radionuclide diagnostic imaging, are complex technologies that require certain infrastructure to be in place before the population of a country can benefit from their application. In many countries where these technologies have been developed and used in clinical practice for some time, the necessary components are already established. These include but are not limited to (a) the manufacture of radiopharmaceutical to a GMP standard, (b) a clear regulatory framework, (c) availability of scanning centres, and (d) suitably qualified personnel.

Countries with less extensive experience in the manufacture of radiopharmaceuticals may encounter several challenges, which, in the first instance, include a basic lack of expertise. In addition, there may also be a lack of clarity with respect to the rules and guidance regarding the process of technological development.

1.2. OBJECTIVE

The primary objective of preparing this publication is to review practices in different countries and to provide recommendations for conducting human studies with new radiopharmaceuticals whose quality, safety and efficacy have already been established. The quality and safety of the radiopharmaceutical should already have been described elsewhere, preferably in a pharmacopoeial monograph. Clinical usefulness should have been reported through the relevant scientific literature and been well documented in clinical practice. Guidance provided here, describing good practices, represents expert opinion but does not constitute recommendations made on the basis of a consensus of Member States.

1.3. SCOPE

The scope of this publication includes a series of recommendations aimed at providing a useful reference to facilitate and expedite the introduction of radiopharmaceuticals in clinical use, in order to provide alternative diagnostic solutions for improved patient care.

For the scope of this publication it is assumed that for a country to introduce a new radiopharmaceutical the necessary infrastructure is already in place, i.e. there is a PET centre with a proximate cyclotron-radiochemistry facility or a nuclear medicine facility with a radiopharmacy.

The IAEA has been proactive in providing expert advice and training resources for those that wish to utilize radionuclides for diagnostic medical use. Comprehensive publications exist on how to set up a clinical PET centre [1] and how to set up a cyclotron facility for FDG production [2] which identifies key issues for the successful implementation of PET related technology. In addition, there is a web-based educational resource on the hospital radiopharmacy set-up and working methods (http://nucleus.iaea.org/HHW/Radiopharmacy/VirRad/index.html).

For the purpose of this document it is assumed that key points in these publications have been addressed or at least are considered by radionuclide imaging communities and regulatory bodies in a country wanting to expand the list of radiopharmaceuticals available for clinical use in their country.

2. NEW RADIOPHARMACEUTICALS

2.1. NEW PET/SPECT RADIOPHARMACEUTICALS FOR CLINICAL USE

The benefits of hybrid imaging are clearly demonstrated in peer reviewed scientific literature and it is now recognized as a routine imaging technique. Hybrid tomography has the unique ability to provide both functional and morphological information at the same time by simultaneous acquisition of PET and computed tomography (CT) / magnetic resonance (MR) or SPECT and CT. Particularly PET/CT imaging, has been one of the fastest growing imaging methodologies over the last decade. Moreover, it has been instrumental in the management of cancer patients, and is a key element in personalized therapy.

The widespread use of PET/CT imaging is also related to the availability of a successful tracer, ^{18}F-Fluorodeoxyglucose (FDG). The reasons for the worldwide use of FDG were both clinical and practical. FDG shows very good diagnostic accuracy, in many oncological settings, and provides important information relevant for patient management. In addition, the production and supply of FDG is now very reliable, with often more than one supplier, and this has certainly assisted its widespread use as a clinical molecular imaging agent. Notwithstanding the almost exclusive use of FDG as a radiotracer in many PET centres (and its many advantages), it does have certain limitations with regards to specificity. It is particularly of limited use in several tumours with a low metabolic rate such as prostate cancer; in well differentiated cancers, such as many hepatocellular carcinomas; in malignancies affecting the urinary tract, such as renal and bladder cancers; or in most mucinous tumours. The mentioned malignancies are frequent around the world, and therefore the need of alternative tracers in oncology is self-evident.

Uptake of FDG in inflammatory and infectious diseases may also be prominent and this could provide an important source of further indications for FDG imaging in benign conditions. However, for oncology patients this can complicate the interpretation of scans, and for this reason there has been a search for more specific PET radiopharmaceuticals in cancer evaluation.

Furthermore, many functional processes such as angiogenesis, hypoxia, apoptosis and others can be evaluated (in vivo) and visualized by means of PET and SPECT tracers. These processes can be extremely important in oncology, but also in other clinical settings. For example, new radiopharmaceuticals targeted at amyloid plaques may be of great importance in the early diagnosis of Alzheimer's disease.

Therefore, there is a clear need for the introduction into clinical use of new PET and SPECT radiopharmaceuticals, which could exploit the limitations of existing tracers and take advantage of a more in-depth knowledge of cancer cell biology. New PET and SPECT radiotracers would also be of benefit in the diagnostic evaluation of heart and brain diseases. There is also a rapidly growing interest in tracers that are aimed at diagnosing infectious and inflammatory diseases.

2.2. BEST AVAILABLE IMAGING METHOD

In the constantly evolving and rapidly changing world of medical imaging, there is an increasing pressure to obtain faster and more accurate diagnosis of chronic debilitating diseases. Modern technology (including hybrid imaging) is pursuing just this by arriving at the correct diagnosis using a single imaging modality, thus mitigating the need for additional imaging as well as exposure to ionizing radiation and associated costs and discomfort.

The use of radiopharmaceuticals can provide insightful information into the nature and mechanisms of disease in a way that was not possible before. It is becoming increasingly clear from scientific publications, that medical imaging with these new radiopharmaceuticals is

potentially more powerful in comparison with both anatomical imaging and traditional nuclear imaging modalities. For example, neuroendocrine tumours can be difficult to image even with the most sophisticated imaging techniques, such as multi-slice CT and MR; however, PET/CT with ^{68}Ga-DOTA-peptides has already been demonstrated to be superior to both conventional imaging and to conventional scintigraphic imaging with ^{111}In-pentetreotide.

It is also important to avoid excessive use of diagnostic imaging procedures in order to reduce both exposure to ionizing radiation, and costs. For example, when recurrence of prostate cancer is suspected, it is not uncommon that transrectal ultrasound, bone scintigraphy, MR with dedicated coil, and whole body CT or MR are utilized on a single patient. However, the use of PET/CT with ^{11}C- or ^{18}F- Choline may be capable of detecting all these lesions with good accuracy, thus reducing the number of requested procedures.

2.3. QUALITY ASSURANCE

A robust quality assurance (QA) system is a prerequisite for the preparation and dispensing of radiopharmaceuticals that are intended for human use. This is discussed in more detail in section 4.6; *good manufacturing practice* (GMP). It is noted that quality assurance and regulatory affairs experts are established members of commercial organizations, however they are not yet routinely available in academic or hospital based clinical imaging facilities. A solid understanding of QA and regulatory affairs are considered to be essential skills required to ensure the smooth and effective implementation of new radiopharmaceuticals.

2.4. TIME AND COST EFFECTIVENESS OF REPLICATION STUDIES

The bio-distribution, dosimetry and safety profile of some radiopharmaceuticals are published in internationally peer-reviewed journals and in addition, their clinical value is also well documented. Under such circumstances these data should be utilized to facilitate and expedite the introduction into clinical practice of new radiopharmaceuticals. This has the immediate advantage of avoiding the repetition of preclinical, phase I and II studies, thus saving a considerable amount of time, resources and money, for the ultimate benefit of the patient. However, the local rules regulating the manufacture and use of radiopharmaceuticals must be observed.

Indeed, the legislation of some countries may require that data are generated locally to demonstrate the validity of the product. Again the scope of this document is not to discuss such an approach, but rather to comment about the real usefulness of replication studies. The need to provide such specific data at a local level is perhaps justifiable when the literature is unclear or if it is to be applied to a new population demographic where mandatory data is absent.

The replication of phase I, II and III studies may not be justified when consistent data is already available (supported by literature) on the use of a radiopharmaceutical.

2.5. KEY COMPONENTS

There are a number of factors that may influence the outcome of introducing a new tracer in routine clinical use. While some are relatively unpredictable, such as contemporaneous development of an alternative approach, most factors can be identified and should be taken into account. The importance of evaluating the pros and cons of a potential new radiopharmaceutical is related to the avoidance costs and time saved, while trying to maximize the likelihood of positive results.

Some factors are applicable to the clinical radiopharmaceutical irrespective of location, such as the diagnostic accuracy of the tracer. However, other factors can be strongly

influenced by local requirements. Therefore, a careful evaluation study is mandatory prior to starting the process of introducing a new tracer.

The key components that will ultimately result in a successful diagnostic radiopharmaceutical are listed in sections 2.5.1 – 2.5.7.

2.5.1. Clinical usefulness

At the outset the clinical utility of a radiopharmaceutical is dependent on the relevance of the clinical question under investigation. A new radiopharmaceutical that can provide important information on a clinical issue is clearly of benefit and likely to be a success; conversely, a tracer providing ancillary data or information not fundamental for patient management is unlikely to be introduced in clinical practice.

Also, it is important to evaluate the relevance of a yet unfulfilled clinical need that the new radiopharmaceutical may address. It may be that other possible approaches are available, with similar diagnostic performance. It is also important to note that a nuclear medicine procedure may require a more complex facility as compared to utilizing other methods. A thorough and critical review of all available literature is therefore required.

2.5.2. Demographic considerations

Demographics can play an important role in the successful introduction of a radiopharmaceutical. Unlike conventional pharmaceuticals, the shelf life of a radiotracer can be short (minutes to hours in the case of PET) and so it is important to have a minimum population base to justify the setup of the facilities required to introduce new products. Furthermore, new radiopharmaceuticals should be initially introduced in areas of higher population density within a geographic region, in order to maximize coverage.

2.5.3. Reimbursement for the diagnostic procedure

An appropriate reimbursement scheme is important for the introduction of a radiopharmaceutical: this should be investigated in advance.

It would be advisable to develop a strategy for defining the criteria of access to reimbursement, in agreement with local agencies and healthcare providers.

2.5.4. Enthusiasm of referring physicians for the service

The decision about using a diagnostic method is always closely associated with clinicians, who rely on several factors, including critical scientific data. It is important that the referring physicians for the scan with the new radiopharmaceutical actively support its introduction. It is essential to have their support and enthusiasm to ensure success.

Therefore, it is of paramount importance to interact positively with the clinical counterparts and to provide adequate support and information on the new product.

2.5.5. Sufficient imaging and reporting resources

The introduction of radiopharmaceuticals will require time on the scanners. It is important that scan time is made available prior to introducing a new product. Some clinical centres may not have sufficient spare capacity to accommodate new imaging protocols so it is fundamental to plan the production and imaging facilities with the necessary resources (including injection rooms).

Furthermore, the availability of the appropriate personnel is crucial, as every step of the process (radiosynthesis, quality control, scan acquisition, exam reporting) will require skilled professionals.

2.5.6. Clinical lead/driver

Every project needs a leader and the same is true with the introduction of a radiopharmaceutical. An individual (often a nuclear medicine physician) needs to take ownership of the project from the outset to its ultimate conclusion. At the same time it is important to have a clear collaboration between all the professionals involved. As compared to other imaging procedures, nuclear medicine methods are more demanding in terms of specifically skilled personnel, including radiopharmacists, physicists and others.

2.5.7. Adequate GMP compliant facility

A GMP compliant facility is a requirement to manufacture radiopharmaceuticals for clinical use in humans. This may require the establishment of a new or separate GMP facility or modifications to an existing facility. This is clearly an important assessment that needs to be determined early in the process.

3. STEPS TOWARDS THE INTRODUCTION OF RADIOPHARMACEUTICALS

3.1. GENERAL RADIOPHARMACEUTICAL IMPLEMENTATION SCHEMA

It is of paramount importance to identify essential steps necessary for the introduction of a radiopharmaceutical in clinical practice, and the sequence of these steps is of equal importance. Each situation is potentially unique and the sequence of steps may vary, nevertheless, it is important to address each step.

(1) Identify radiopharmaceutical;

(2) Conduct literature search;

(3) Formulate questions / proposal for regulators;

(4) Identify synthesis process for radiopharmaceutical;

(5) Prepare a submission package for regulatory submission;

(6) Confirm plan with regulators;

(7) Obtain financial resources;

(8) Validate manufacture process;

(9) Submit a dossier to regulators;

(10) Identify and validate sites (if confirmatory trial needed);

(11) Initiate trial and analyze data (if confirmatory trial needed);

(12) Formulate and submit final results;

(13) Receive regulatory approval;

(14) Start routine medical use;

(15) Evaluate with referring clinicians the appropriate use.

3.1.1. Identify radiopharmaceutical

The identification of a radiopharmaceutical is obviously the first step of the process. Indications about the criteria to use for identification are provided in section 4.1. It can be difficult to predict effective and successful new tracers for future use and so it is important to be aware of yet unfulfilled diagnostic needs and the clinical relevance of the potential information that could be generated.

3.1.2. Literature search

Some suggestions for the necessary criteria for performing a literature review are provided in section 4.2. In general it is advisable to perform a robust data analysis, and a cost effectiveness evaluation.

3.1.3. Formulate questions/proposal for regulators

An outline proposal for the radiopharmaceutical should be submitted to the local regulatory authority. The proposal should address if the existing literature is adequate or if a confirmatory trial is needed for approval. Interaction with the competent regulatory authorities is fundamental. A collaborative approach is essential and in most cases they are very keen to participate in the process.

3.1.4. Identify synthesis process for radiopharmaceutical

It is highly advisable to use an already described synthesis process in the manufacture of a new tracer. It is recommended to obtain the synthesis module from a vendor that has developed the system to GMP standards for the tracer of interest. Also quality attributes may be already available in a pharmacopoeia.

3.1.5. Prepare a submission package for regulatory submission

The process of interactive discussion with regulators may lead to the conclusion that confirmatory data are not necessary, thus avoiding the need for further trials. However, even in these circumstances, a regulatory submission package has to be prepared. Should the regulations prescribe a confirmatory trial, a detailed protocol has to be prepared.

3.1.6. Confirm plan with regulators

Before progressing any further, it would be beneficial to receive positive feedback from the regulators.

3.1.7. Obtain financial resources

The production of radiopharmaceuticals is expensive and there are additional costs associated with the introduction of a new imaging agent. This may include any of the following:

- Clean room facility;
- Gowning lobbies;
- Quality control laboratory space;
- Hot cells;
- Synthesis modules;
- Quality control equipment (HPLCs, GCs);
- Additional staff resources (radiochemistry, medical, etc.);
- Source for radionuclides (cyclotron, target, generator or commercial supplier).

In case a confirmatory trial is required by regulators, further resources may be needed to support trial-related costs.

3.1.8. Validate manufacture process

The manufacturing process should be validated in accordance with GMP (section 4.6).

3.1.9. Submit a dossier to regulators

A compilation of all of the results should be submitted to the regulatory authorities (Investigational Medicinal Product Dossier (IMPD) or similar).

3.1.10. Identify and validate sites (if confirmatory trial needed)

As mentioned in 3.1.5, it may be that regulators will require a confirmatory trial to be performed, and this may necessitate that both manufacturing and imaging validation studies should be performed at all trial sites. See Appendix III for examples of conducting clinical trials in different countries.

3.1.11. Initiate trial and analyze data (if confirmatory trial needed)

The trial has to be carried out according to the approved protocol, the data then has to be analyzed and reported.

3.1.12. Formulate and submit final results

Submission of all results is mandatory to proceed further.

3.1.13. Receive regulatory approval

The goal of the process should be the approval of the clinical use of the radiopharmaceutical from the regulatory authority.

3.2. FLOW CHART

The flowchart on the next page (Fig. 3.1) covers the many possible routes for introducing a radiopharmaceutical; it includes routes that are not covered in the rest of this publication (experimental use of potential diagnostic agents) for the sake of completeness.

It is important to complete the background research into an existing product before approaching the local regulatory agency.

The first step is to gather product information, including existing licensed manufacturing of the product, pharmacopoeia references and any other pertinent manufacturing and control documentation. Some regulatory agencies may accept peer-reviewed publications as part of the application/discussion process.

For existing radiopharmaceuticals, there will be some evidence of clinical use. The extent of use and evaluation of the medical usefulness will vary considerably between products. Consideration should be given to the patient population demographics and previous licensing requirements of the product elsewhere. For a product which has been licensed in an ICH participant area (where comprehensive clinical trials will be required before a license is issued), there should be minimal barriers to implementation; however local requirements may include the need for confirmatory studies to demonstrate safety and efficacy in the local population and/or that the manufacturing process produces an equivalent product to that licensed elsewhere.

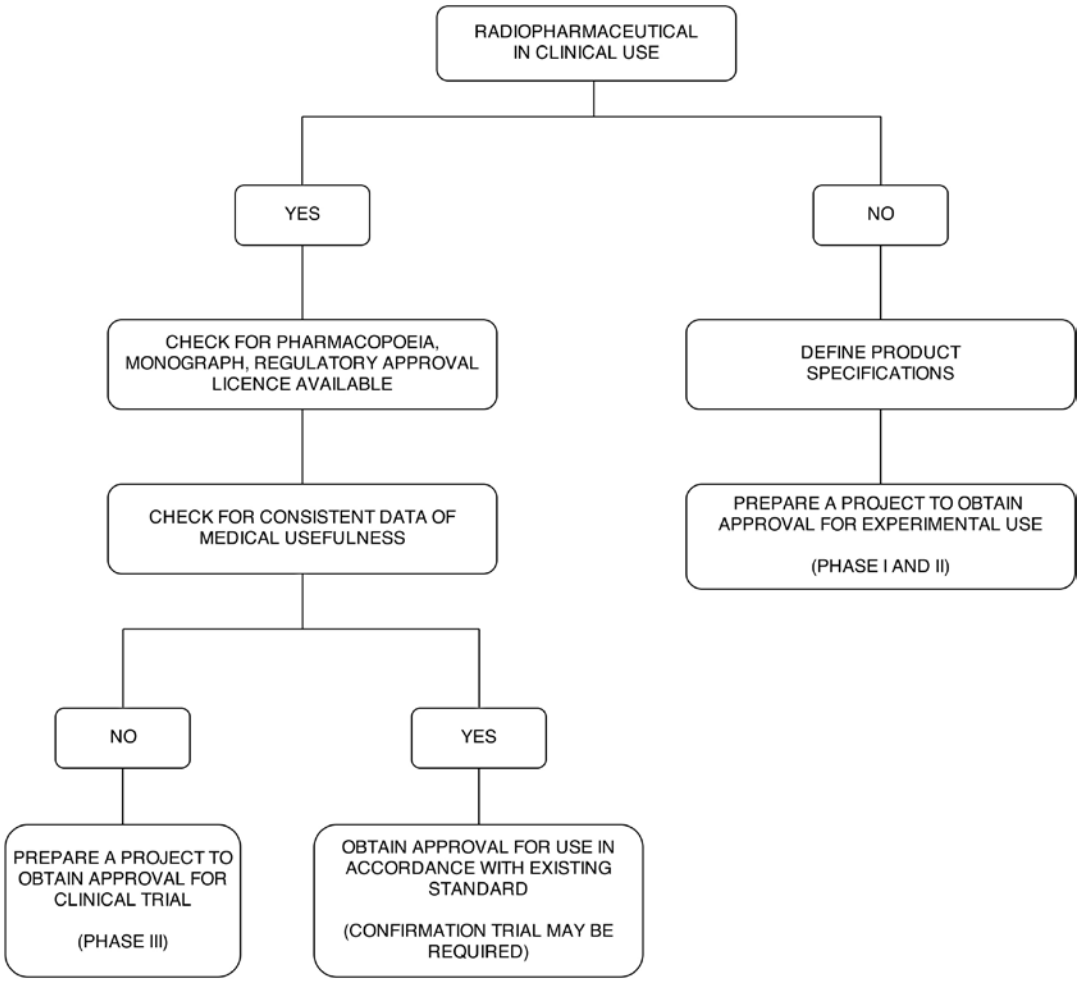

FIG. 3.1. Possible routes for the introduction of a radiopharmaceutical.

It is not possible to give a comprehensive assessment of how local regulatory agencies will respond to proposals for the introduction of a diagnostic radiopharmaceutical. It is therefore vital that the manufacturer communicates effectively with their local regulators. The manufacturer needs to have an understanding of the local requirements for manufacture and approval of this type of product to ensure that they can build confidence with the regulators in their introduction of the product.

Regulatory agencies are established to protect the public health and usually communicate with commercial pharmaceutical companies who have dedicated staff for this process. Non-commercial manufacturers should be aware of the specialist knowledge and language required in these communications and account for that in their approach, seeking expert advice or training individuals for this role.

The specific requirements to achieve approval for the manufacture of the radiopharmaceuticals are the responsibility of the local regulators. The manufacturer must comply with any and all requirements imposed by these authorities. Good communication with the agency will ensure that these requirements are scientifically sound, risk appropriate and not onerous.

4. IDENTIFICATION AND EVALUATION OF DATA

4.1. IDENTIFICATION

Typically, the national nuclear medicine society would be the primary organization involved in the selection of a new radiopharmaceutical being introduced into a country. The role of national and international scientific societies is very important and should be supportive of the whole process. Alternatively, a specific institution or company might also choose to introduce a new agent. In either case, there should be an open discussion about the clinical relevance of the selection to ensure that there is widespread support and high likelihood of success.

Currently the most likely candidates include somatostatin receptor ligands (^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE or ^{68}Ga-DOTANOC), lipid synthesis agents (^{18}F-choline) and amino acid transport tracer (^{18}F-DOPA). It is important to underline that the scientific literature in the area of PET and SPECT is growing very rapidly, and many potential new tracers have been proposed in recent years. Therefore, this short list is just intended to summarize the opinion of the meeting participants (August 2013).

Other possible radiotracer candidates could be other lipid synthesis agents (^{11}C-choline and ^{11}C-acetate), other amino acid transport tracers (^{11}C-methionine, ^{123}I-alpha amino tyrosine, ^{18}F-FET), myocardial perfusion (^{13}N-ammonia), hormonal receptor agents (^{18}F-fluoroestrogen, ^{18}F-FHDT), hypoxia agents (^{18}F-FMISO, ^{18}F-FAZA, ^{64}Cu-ATSM), dopaminergic and adrenergic ligands (^{18}F-fallipride, ^{11}C-raclopride, ^{11}C-spiperone, ^{11}C-mHED), proliferation tracers (^{18}F-FLT) and bone seeking tracers (^{18}F-NaF).

4.2. EVALUATION OF EXISTING DATA OF MEDICAL USEFULNESS

As already stated, the present recommendations are not intended for conducting phase I or II studies. The possible radiopharmaceutical to be introduced in clinical practice should have completed phase I and II studies: as such, safety and dosimetry should have been already completely addressed. Subject to acceptance by local regulatory agencies, it is clearly advantageous to consider using existing data both on safety and dosimetry that has been generated in nations that have mutually recognized regulatory frameworks.

Efficacy studies (phase III or similar) should have already been done to demonstrate the usefulness of the agent, and in particular the diagnostic accuracy of the radiopharmaceutical. For some of these new radiopharmaceuticals, it is acceptable that efficacy studies have been performed not as a prospective multi-centers trial (phase III) but also as separate retrospective large population trials, published in international peer reviewed journals. Such data may be sufficient for submitting an application for approval of a radiopharmaceutical for clinical use.

It is preferable if the proposed radiopharmaceutical is already described in a pharmacopoeia standard (such as ^{68}Ga-DOTATOC); or approved in some country for clinical routine use (such as ^{18}F-FDOPA); or been licensed for commercialization of the tracer in some country (such as ^{18}F-Choline).

One of the first steps in considering the introduction of a radiopharmaceutical is a careful review of the relevant literature. It may be preferable to have this performed by external experts, with expertise in meta-analysis. The procedures for correctly performing a systematic review of medical data are widely known. In some cases, such review could be already available and up to date. For example, a meta-analysis of the use of ^{18}F-DOPA in patients with paraganglioma has been published in the European Journal of Nuclear Medicine [3]. In other cases, the review might exist but may not be up to date and may need to be reviewed. For example, a meta-analysis of the use of fluoride PET (^{18}F-NaF) has been published in Annals of Nuclear Medicine [4].

It is relevant that a review analysis should take into account the use of a specific radiopharmaceutical in a clearly defined clinical scenario. It should generate aggregate data in a tabulated manner that enables the estimation of pooled sensitivity and specificity. Examples of such an approach are widely available for diagnostic use of PET with many oncological indications.

4.3.POSSIBLE PARTNERSHIP

The successful implementation, viability and sustainability of reliable production and supply of radiopharmaceuticals are dependent on a number of key factors, including but not limited to:

- Medical expertise;
- Radiochemical expertise;
- Appropriate manufacturing and imaging capabilities;
- GMP and *good clinical practice* (GCP) expertise and compliance.

It may be the case that a single institution does not have the breadth of capabilities to cover all of these requirements and under these circumstances it may be appropriate to harness the various skillsets and infrastructure in a partnership arrangement that satisfies the needs of all stakeholders. Examples of such collaborations could include:

- Public-Private partnerships;
- University and Hospital collaborations.

4.4. REGULATORY AUTHORITIES

Regulatory agencies are established to protect the public health. At the outset, it is essential to interact with the local regulatory authorities to ensure that all key requirements are taken into consideration.

The largest sector with which they work are commercial pharmaceutical companies who have dedicated staff, experienced in regulatory affairs, medicines development and quality assurance to facilitate the introduction of new pharmaceuticals. Radiopharmaceuticals constitute a very small, specialized sector with which they may not have familiarity with and therefore good communication is essential to ensure that appropriate requirements are established for the progression of the approval process.

Non-commercial manufacturers should be aware of the specialist knowledge and language required when communicating with regulatory agencies and account for that in their approach, seeking expert advice or training individuals in their organization especially for this role.

It may be possible to use professional bodies or other government agencies as intermediaries to facilitate good communication with the regulators and establish appropriate processes for the consistent application of appropriate regulations.

4.5. RADIOPHARMACEUTICALS NOT INCLUDED IN PHARMACOPOEIA

It may be the case that not all countries or geographical regions will have access to an approved pharmacopeia of their own. Indeed, it may be that not all pharmacopeias will have a section on radiopharmaceuticals. Under these circumstances, the introduction of a new radiopharmaceutical will be all the more demanding. Even in countries that have a national

pharmacopeia with a general section on radiopharmaceuticals, it is possible that radiopharmaceuticals approved for routine diagnostic use are yet to be incorporated.

A more rapid incorporation of established radiopharmaceuticals into pharmacopeias would be of great benefit to the introduction of new radiopharmaceuticals. Nevertheless, the present recommendations can be applied for those radiopharmaceuticals not currently in a pharmacopoeia. In such case it is the responsibility of the manufacturer to justify the specifications of the product.

4.6. GOOD MANUFACTURING PRACTICE

Good manufacturing practice (GMP) guidelines have evolved over the last 50 years with the global pharmaceutical industry and during this time GMP compliance has become compulsory for the manufacture of pharmaceuticals (and radiopharmaceuticals). It is part of the quality assurance system related to the manufacture of a product and it endeavors to ensure that products are consistently manufactured to a quality appropriate for their intended use. The quality of the finished product must meet the required quality standards 100% of the time and the key components that underpin the product quality are:

- Safety;
- Efficacy;
- Purity;
- Uniformity.

The key rationale for this approach is that:

— A patient is unlikely to know if the quality of the product does not meet the required standard (i.e. defect may not be visibly obvious);
— Samples of product are tested, leaving the majority of the batch untested;
— A product defect could be potentially very dangerous for patients, even if a very small number of items in a batch are defective.

The GMP regulations are very detailed and it is essential that the local requirements are thoroughly understood. In essence they describe a set of activities and controls that ensure that drug products are consistently manufactured to meet a required specification. These regulations can be summarized under the following general headings:

— People (personnel);
— Premises (and equipment);
— Paperwork (documentation);
— Processes (control of production processes);
— Products (sampling and testing).

GMP is a requirement for the manufacture of a radiopharmaceutical and it should be adopted from the outset considering all of the potential regulatory requirements. In the absence of local GMP regulations, it may be advisable to refer to the World Health Organization (WHO) GMP guidance [5].

4.7. RISK MANAGEMENT

Risk management is an integral part of pharmaceutical development and has been incorporated into regulatory requirements through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Quality Risk Management (ICH Q9) (Fig. 4.1). A comprehensive risk-based approach to the implementation of a radiopharmaceutical will ensure that:

- All of the factors affecting the project will be taken into consideration;
- The manufacturing process will be efficient;
- The manufacturing process will be compliant with regulations;
- The licensing process will be as efficient as possible;
- Discussion with regulatory agencies will be risk appropriate and scientifically sound;
- Regulatory agencies will have confidence in the capability of the manufacturer.

The principals outlined in ICH Q9 are applicable throughout the development, implementation and ongoing manufacture of the product.

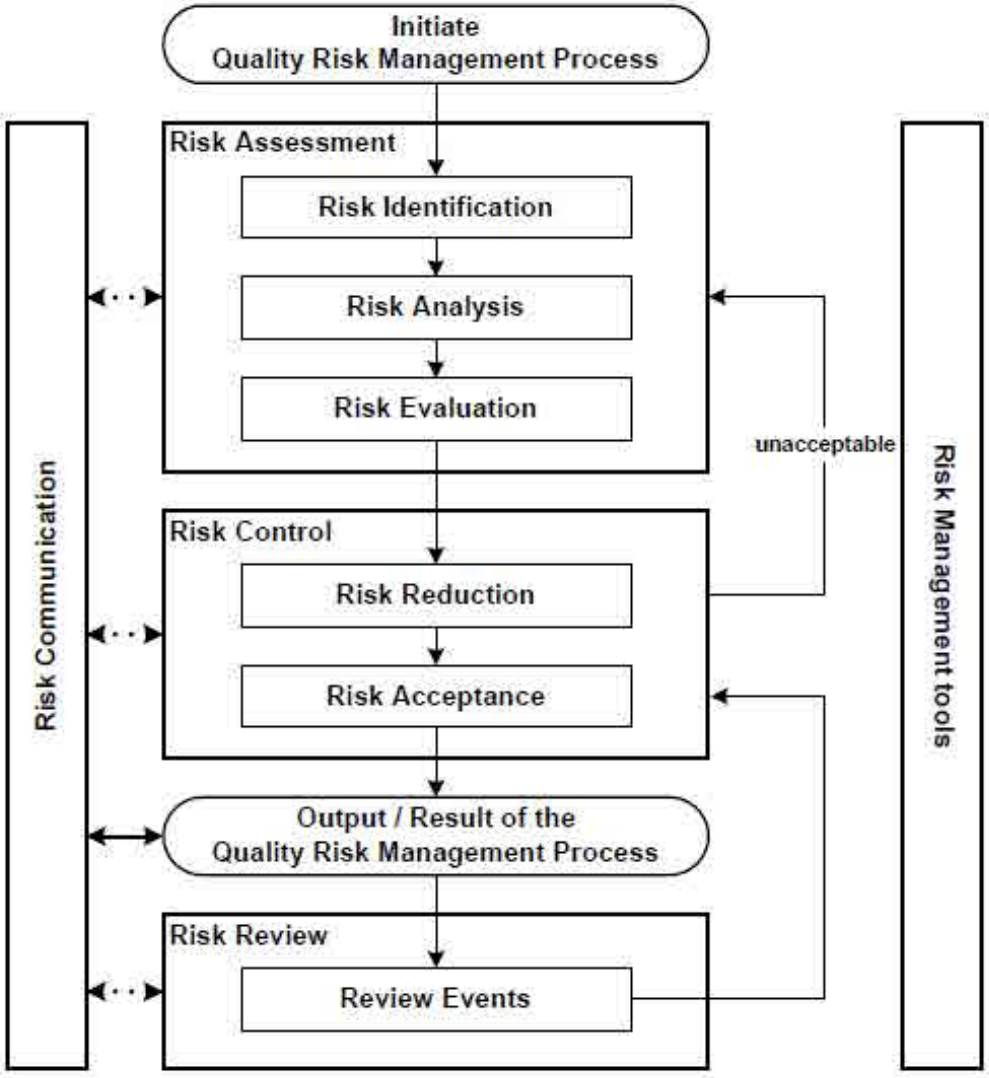

FIG. 4.1. Regulatory requirements through ICH Q9.

4.8. MEDICAL ISSUES

4.8.1. Definition of clinical indication

It is essential that the radiopharmaceutical addresses a specific, well-defined clinical indication. In general, a referring physician proposes a specific clinical question that the diagnostic procedure is planned to address. The nuclear medicine physician evaluates the request and agrees that the indication is correct and appropriate. An example would be the use of ^{18}F- or ^{11}C-choline in the diagnosis of sites of metastatic disease in the setting of recurrent prostate cancer with rising prostate-specific antigen (PSA).

The identification of guidelines for appropriate use of PET and SPECT scans has been addressed by several *health technology assessment* agencies, on the basis of evidence-based medicine approach. For example there are many recommendations regarding the criteria for the use of FDG PET [6]. A similar process is expected to be performed for any new radiotracers after clinical use is established.

When introducing a new radiotracer, the definition of appropriate clinical use must be addressed. Some indications may be already clear at the outset, such as lab recurrence (rising PSA) of prostate cancer for ^{18}F-choline PET, while others may be limited to the object of the clinical trial (such as evaluation of primary CNS malignancy with ^{18}F-choline PET).

4.8.2. Imaging requirements

Nuclear medicine images obtained with PET or SPECT consists of multi-dimensional datasets of counts / pixel (or counts / voxel), and the dataset directly reflects regional concentration of radioactivity. Thus, nuclear medicine is a quantitative technique for the detection of molecular interaction of a radiopharmaceutical with the endogenous target. However, its quantitative power for clinical research can only become productive when there is strict standardization of imaging protocols. Additionally, quality control (QC) / quality assurance (QA) procedures must be in place to ensure that optimal quantitative images and data are acquired.

In either clinical trials or routine clinical use of PET/SPECT, imaging consistency (standardization) is crucial. To realise such consistency, it is essential that baseline common quality control metrics for PET/SPECT scanners used in PET/SPECT communities should be established.

The IAEA has published guidelines for quality assurance of SPECT systems [7] and efforts for global harmonization of PET standardization have been performed under the collaboration of various professional organizations, such as the Society of Nuclear Medicine and Molecular Imaging (SNMMI) (http://interactive.snm.org/index.cfm?PageID=10641). These publications / activities can be helpful for achieving adequate PET/SPECT imaging studies.

4.8.3. Personnel training

All personnel involved in the process should have adequate training; in particular physicians, technologists and nurses need to have appropriate training and an understanding of the radiopharmaceutical in order to use it effectively. There are numerous resources available on the IAEA web site as well as on the SNMMI and European Association of Nuclear Medicine (EANM) websites.

It is important to understand that before planning the introduction of a new radiopharmaceutical into clinical practice, that personnel must receive the appropriate training required for the specific tracer. While a relevant background in the field is mandatory,

training in an approved imaging and patient management protocol must be provided and adhered to. In most cases this can be achieved by training and visiting reference sites (often supported by the IAEA) and through local training by experts.

4.8.4. Education and informing referring physician

It is essential that the relevant referring physicians are involved as early as possible in the selection of a new radiopharmaceutical, as well as in defining the most likely clinical settings where it is useful. Some time may elapse between the selection of a new agent and its availability. It is important to maintain contact with the referring physicians during this time to ensure continuing interest. Once an agent has been selected and approved for clinical use, it is useful to increase the engagement with referring physicians through lectures, seminars, patient management meetings and departmental meetings.

4.9. MAGISTRAL AND OFFICINAL PREPARATIONS

It is recognised that all countries may not have a clear regulatory framework in place to facilitate the introduction of a non-licensed radiopharmaceutical for clinical studies. In this case, the provisions for the 'magistral / officinal formula' can be considered to facilitate the introduction of useful diagnostic radiopharmaceuticals into clinical practice.

Historically, magistral and officinal preparations have evolved from the practice of formulation by a licensed pharmacist in accordance with the prescription of a doctor for the named patient. Thus, the notion of magistral and officinal preparations creates a direct link between the doctor, pharmacist, quality of a drug and the patient. The doctor takes responsibility for the prescribed pharmaceutical, and the pharmacist is responsible for the quality of the prepared pharmaceutical.

The introduction of magistral and officinal preparations does not exempt the manufacture of radiopharmaceuticals from the GMP requirements. It does however provide a practical approach for practitioners to introduce novel radiopharmaceuticals safely into clinical practice.

Magistral and officinal preparation arrangements apply only for in-house use, i.e. radiopharmaceuticals produced by a radiopharmacy should be manufactured under *good laboratory practice* (GLP) standard, in accordance with a medical prescription and supplied directly to the patients served by this radiopharmacy. Certain conditions should be fulfilled in order for these arrangements to be effective.

1) Clear provisions must be laid down for a medical prescription by a nuclear medicine physician for an individual patient;
2) The radiopharmaceutical must be manufactured under the supervision of a licensed radiopharmacist in accordance with validated procedures (magistral preparation);
3) When the product follows the prescription of a pharmacopoeia monograph this is called an officinal preparation;
4) The facility which intends to manufacture radiopharmaceuticals using magistral / officinal formula arrangements should meet all the necessary local regulations required to produce radiopharmaceuticals. The expected quality standard should meet GMP requirements (see 4.6);
5) Radiopharmaceutical must be supplied to the patients to whom it was prescribed for by a nuclear medicine physician and served by the radiopharmacy. The regulatory licence should be issued by the local regulatory authority for in-house use;

6) A licensed radiopharmacist is required to release the product for patient use in accordance with approved procedures (see Appendix IV for *product release criteria*). An example of the *product specification file* (PSF) is provided in Appendix V;
7) The laboratory must maintain all manufacturing and patient records for an approved period of time (i.e. 5 years).

4.10. POTENTIAL LIMITATIONS

Potential barriers to the medical use of a new radiopharmaceutical can be due to pharmaceutical, clinical, administrative or financial causes.

1) Potential radiopharmaceuticals manufacturing issues:

   — The manufacture of a pharmacologically active molecule can be a very complex process;
   — A manufacturing process that involves potentially harmful intermediates / additives whose absence / presence below permissible limits can be difficult to demonstrate;
   — The manufacturing process may not have been approved by local authorities;
   — Purity standards may not have been defined using well-established analysis techniques;
   — Precursors as well as end product (radiopharmaceutical) may be locally covered by patent, and thus not widely available;
   — Radionuclide generators and pre-cursors importation may be limited by local regulations.

2) Potential clinical issues:

   — If study data submitted is of experimental / phase I only / incomplete phase II / inconclusive phase II, or if the design had a limited number of subjects;
   — If local authorities do not approve the study;
   — If all the study procedures, such as the protocol, investigators brochure, informed consent forms and others, are not yet complete.

3) Potential administrative issues:

   — If the radiopharmaceuticals infringe a local law (e.g. blood derivatives);
   — Studies where Head of Institute, Head of Department, or Principal Investigator do not give written consent;
   — If patients participating in a trial / study are not covered by appropriate liability insurance.

4) Potential financial issues:

   — Arrangement based on profit needs to be excluded for the trial period / pre-approval. However, the recovery of costs may be feasible, if allowed by local regulators.

4.11. CONCLUSIONS

The introduction and use of new radiopharmaceuticals would ideally have a very positive impact on diagnostic imaging and therefore on patient management. Notwithstanding the fact that many countries have developed a reliable technology for the production and distribution of radiopharmaceuticals, there are still difficulties associated with the specific rules and approvals for conducting studies with radiopharmaceuticals.

These recommendations for introducing radiopharmaceuticals for clinical use provide an overview of practices in different countries and regions. It also details the principles for introducing radiopharmaceuticals whose safety and efficacy have been established through the relevant scientific literature and documented clinical practice.

These recommendations are intended to provide a useful reference to facilitate and expedite the introduction of radiopharmaceuticals into clinical use with the result of beneficial diagnostic solutions for improved patient care.

It is important to maintain a balance between ensuring the highest level of patient safety while at the same time facilitating reliable access to innovative technologies with improved patient care. The QA, GMP and risk assessment rules always have to be respected and the studies have to be carried out in compliance with international standards. However, it is also important to optimize time and cost by avoiding replicate studies that generate duplicate sets of data.

A general schema of the process implementation is provided, along with a suggested flow-chart. The most important issue, however, is to foster a positive collaboration between all of the stakeholders, namely the professionals (nuclear medicine physicians, radiopharmacists, physicists etc.), regulatory representatives and possible external partners (universities and industries).

5. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER
^{18}F-SODIUM FLUORIDE INJECTION

5.1. INTRODUCTION

This clinical trial application presents information relating to ^{18}F-Sodium Fluoride ([^{18}F]NaF) injection containing 100 – 500 MBq of Fluorine-18 (as the sodium salt) at the time of injection. [^{18}F]NaF is a marker of bone turnover in positron emission tomography (PET) and is being developed for the sensitive detection of bone metastases.

*5.2.*CHEMICAL PHARMACEUTICAL AND BIOLOGICAL DATA

5.2.1. Drug substance

5.2.1.1. General information

Nomenclature

Chemical name (IUPAC)	[^{18}F]sodium fluoride
Code name	[^{18}F]NaF injection
Other names	Sodium fluoride-F18
Structure	
Structural formula	[^{18}F]NaF
General properties	
Molecular formula	
Molecular weight	Note that macroscopic physico-chemical properties of the drug substance have no relevance, as this is a carrier-free radiopharmaceutical and will be produced only in aqueous solutions with specific activities ranging 50-500 GBq/µmol.
Chirality/stereochemistry	Not relevant
Description	A non-carrier added radiopharmaceutical preparation, inorganic salt. ^{18}F decays with the half-life of 109.8 minutes and emission of positron radiation with a maximum energy of 0.633 MeV, followed by photon annihilation radiation of 0.511 MeV.
pH and pKa	Not relevant.
Melting point	Not relevant.
Solubility	The solubility of [^{18}F]NaF in water is the same as that of sodium fluoride 4.13 g/100 g (25 °C).
Hygroscopicity	Not relevant, as the product is an aqueous solution.
Crystal form	Not relevant.

5.3. MANUFACTURE

5.3.1.1.Manufacturer(s)

The drug substance, [^{18}F]NaF injection, is manufactured in accordance with GMP at the following facility:

Company Name:

Street address:

Town:

Country:

5.4. DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

5.4.1. Synthetic route

[^{18}O]water is irradiated in the liquid target of a medical cyclotron with 10-40 μA beam of protons with an energy of 16MeV. The nuclear reaction leading to the production of [^{18}F]fluoride is described as $^{18}O(p,n)^{18}F$. The obtained water solution of [^{18}F]Fluoride is passed through the anion-exchange solid phase extraction cartridge to trap [^{18}F]Fluoride. The cartridge is rinsed extensively with water for injections to remove all the possible water-soluble impurities. The [^{18}F]NaF is obtained by rinsing the anion-exchange cartridge with the sterile physiologic saline solution.

A flow diagram for the synthesis of [^{18}F]NaF injection is provided in Fig. 5.1 including starting materials, intermediates, solvents and reagents for each stage.

5.4.2. Synthetic route for batches used in nonclinical studies

Non-clinical studies represent manufacturing process development including quality control method development. No preclinical studies were conducted because the product is well characterized in the literature and has been extensively used in the nuclear medicine clinical practice elsewhere around the world. Two representative development batches of [^{18}F]NaF (NaF-1260 and NaF-1263) are reported here. These batches were manufactured according to the flow diagram provided in Fig. 5.1.

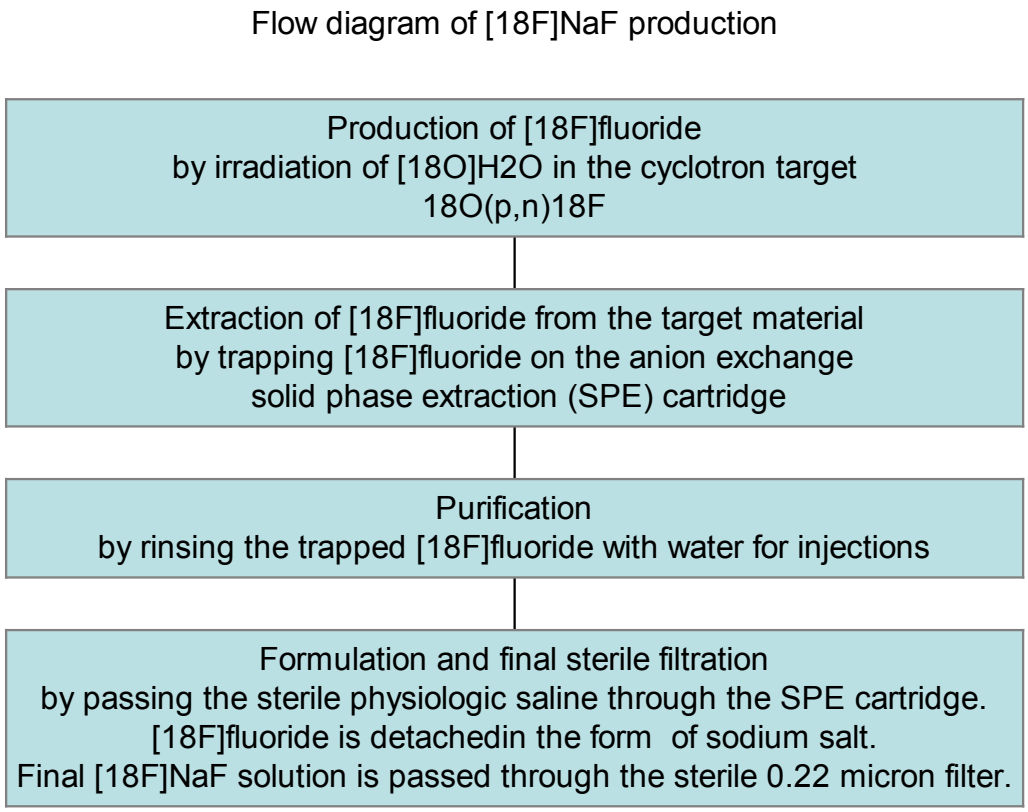

FIG. 5.1. Flow Diagram for the Synthesis of [^{18}F]NaF injection

5.4.3. Control of materials

Development of the synthesis of the active ingredient is still at an early stage. Appropriate specifications for the starting materials and intermediates are not yet available but will be established as more experience of the manufacturing process is obtained. Where possible, the pharmaceutical grade starting materials will be used.

5.4.4. Controls of critical steps and intermediates

No intermediates exist in the manufacture of the drug substance. The critical step is irradiation of the enriched water in the cyclotron target. This process is well developed and characterized in the manufacture of other clinical radiopharmaceuticals (e.g. [^{18}F]FDG). The main control is the target yield of [^{18}F]fluoride.

5.4.5. Process validation and/or evaluation

No information yet available.

5.4.6. Manufacturing process development

Development production batches No. NaF-XXX and NaF-YYY were successfully produced with the following product characteristics (Table 5.1.).

TABLE 5.1. PRODUCT CHARACTERISTICS

Batch No	Radiochemical Purity	Specific Radioactivity	pH
NAF-XXX	100%	397.6 GBq/μmol	7.5
NAF-YYY	100%	140.5 GBq/ μmol	7.5

5.4.7. Elucidation of structure and other characteristics

Product NaF-XXX was produced following the route of synthesis presented in Fig. 5.2. High performance liquid chromatography (HPLC) studies performed (Fig. 5.2 – 5.4), were consistent with the assigned chemical structure.

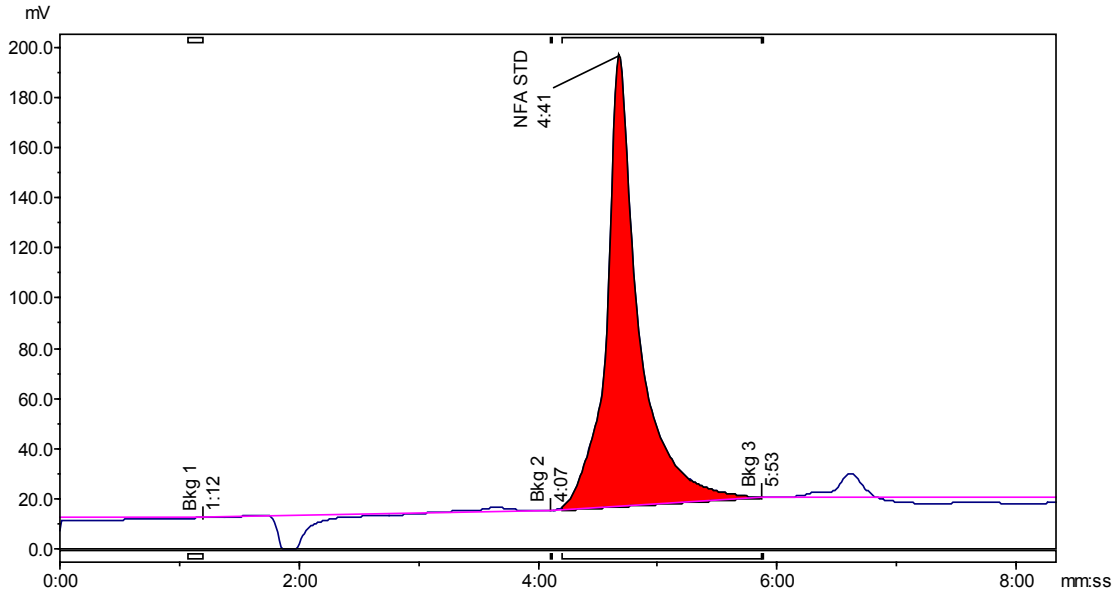

FIG. 5.2. EC Chromatogram of NaF standard

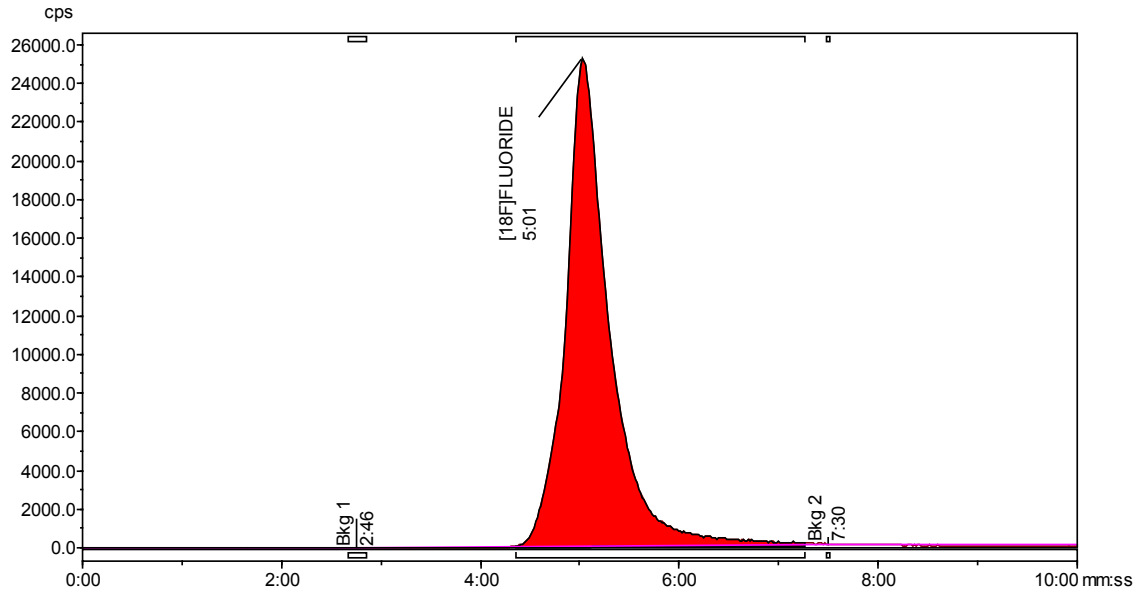

FIG 5.3. Radio-chromatogram of NaF-1263 sample

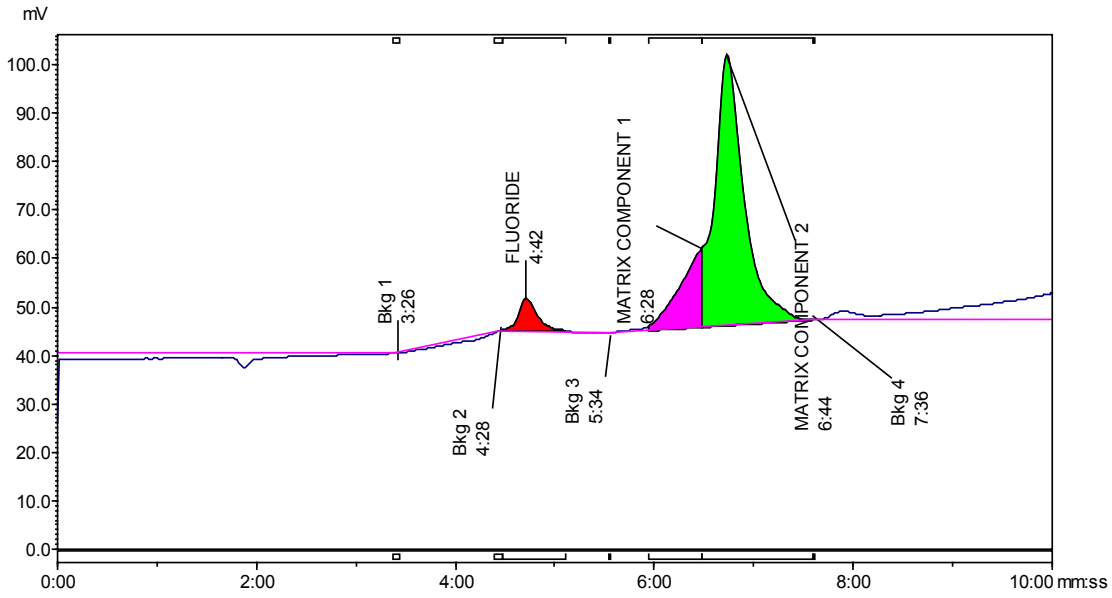

FIG 5.4. EC chromatogram of NaF-1263 sample

These data were generated using [^{18}F]NaF injection batch NaF-XXX, which was manufactured according to the flow diagram in Fig. 5.1.

TABLE 5.2. IDENTITY TESTING OF [^{18}F]NaF INJECTION (BATCH NaF-XXX)

	Retention time on HPLC	
Injected sample	Reference Standard	Sample injection NaF-XXX
NaF	4:41	4:42
[^{18}F]NaF		5:01

The chemical identity was confirmed by comparison of HPLC injection with the reference standard. All chromatograms obtained were co-eluting with the reference standard of sodium fluoride.

The gamma spectroscopic data and half-life measurements for radionuclide identity are not available yet and will be presented later.

5.4.8. Impurities

5.4.8.1.Potential impurities from the synthesis and degradation of [^{18}F]NaF injection

There are no potential drug-related impurities in the [^{18}F]NaF injection as the drug represents a stable inorganic salt.

5.4.8.2.Potential impurities which may arise during irradiation

In the cyclotron target there are other radionuclides which are controlled by the specification (> 99% radionuclidic purity) for [^{18}F]NaF injection, the most likely radionuclide impurity would be ^{13}N (half-life 10 min) produced by a side nuclear reaction ^{16}O(p,α)^{13}N from the normal O-16 water contained in the O-18 enriched target water material. Radionuclide purity data will be collected during validation studies.

5.4.9. Control of drug substance

5.4.9.1.Specification

Batches of the active ingredient will comply with the following specification (table 5.3). Batches will be released for clinical trial purposes only if the impurity profiles can be supported by available non-clinical data.

TABLE 5.3. SPECIFICATION FOR [^{18}F]NaF INJECTION

Test	Acceptance criteria
Description	Clear, colourless solution
Identification	
[^{18}F]NaF injection by HPLC	The retention time of the sample is concordant with that of the NaF reference standard
[^{18}F]NaF injection radiochemical purity by HPLC (%)	Greater than 98.5
Radionuclide purity by half-life determination (min)	110±5 min
Any unqualified impurity (%)	Not greater than 10% of the major non-radioactive peak on HPLC *(limit to be defined based on dosing considerations)*
Total impurities (%)	Not greater than 10% of the major non-radioactive peak on HPLC.

5.4.9.2.Analytical procedures

The methods used to control the drug substance are summarized below. In the course of ongoing developments, analytical methods will continue to be optimised, and revised methods will be implemented and appropriately validated.

5.4.9.3.Description of [^{18}F]NaF injection

A sample of the drug substance is examined for physical form and colour.

5.4.9.4.Identification of [^{18}F]NaF injection by γ-HPLC

The radio-chromatogram is recorded of the sample spiked together with the authentic reference standard of sodium fluoride. The retention time of the sample on the radioactivity detector trace is compared to that of an authentic reference standard on the conductivity detector trace to ensure that it is concordant (with the correction of the time difference due to dead-volumes between radioactivity and conductivity detectors).

5.4.9.5.[^{18}F]NaF injection content by HPLC

The method for determination of [^{18}F]NaF injection content is an isocratic anion-exchange-phase HPLC method, using a Carbopack column, or suitably validated alternative. The mobile phase is a mixture of sodium hydroxide and water, with conductivity detection.

5.4.9.6.Radiochemical impurities content of [^{18}F]NaF injection by HPLC

The method for determination of [^{18}F]NaF injection content is an isocratic anion-exchange-phase HPLC method, using a Carbopack column, or suitably validated alternative. The mobile phase is a mixture of sodium hydroxide and water, with radioactivity detection.

5.4.9.7.Validation of analytical procedures

Only brief details of the validation performed are reported. There will be sufficient validation data in place to assure that the methods are suitable for use according to the *quality assurance systems* (QAS) in place at the manufacturer's site.

5.4.9.8.[^{18}F]NaF injection content by HPLC

Validation of the method has been carried out to demonstrate specificity, linearity and repeatability.

5.4.9.9.Radiochemical impurities content of [^{18}F]NaF injection by HPLC

Validation of the method has been carried out to demonstrate specificity, repeatability and the limit of detection (LOD) for each significant drug-related impurity. (The LOD will be provided for significant drug-related impurities).

5.4.9.10. Batch analysis

Batch analysis data are presented in Table 5.4 for two batches of [^{18}F]NaF injection manufactured for non-clinical use, using the synthetic route provided in Fig. 5.1.

TABLE 5.4. BATCH ANALYSIS DATA FOR BATCHES OF [^{18}F]NaF INJECTION

Batch number		NAF-YYY	NAF-XXX
Batch size (GBq)		1.6	1.4
Place of manufacture		AAAAA	AAAAA
Date of manufacture		DD/MM/YY	DD/MM/YY
Use		Non-clinical	Non-clinical
Test	Acceptance criteria		
Description	Transparent colourless solution	Transparent colourless solution	Transparent colourless solution
Identification			
[^{18}F]NaF injection by HPLC	The retention time of the sample is concordant with that of the NaF reference standard	Conforms	Conforms
[^{18}F]NaF injection radiochemical purity by HPLC (%)	Greater than 95	100	100
Other impurities content by HPLC, (% area)			
Any unqualified impurity	Not greater than 10		
Total	Not greater than 10	0	0

5.4.9.11. Reference standards or materials

Reference standard of NaF was purchased from Fischer Chemical (Code: J/4548/06) Batch Number xxxxx.

5.4.9.12. Container closure system

[^{18}F]NaF injection is stored in a sterile glass vial, sealed with a rubber stopper, and placed in lead containers.

5.4.10. Stability

5.4.10.1. Decomposition chemistry

Decomposition chemistry is not relevant for [^{18}F]NaF injection as sodium fluoride is an inorganic salt and is known to be one of the most stable chemical compounds.

The radioactive isotope ^{18}F decays with the half-life of 109.8 minutes and emission of positron radiation with a maximum energy of 0.633 MeV, followed by photon annihilation radiation of 0.511 MeV. This photon radiation is used in PET for quantitative registration in the medical PET scanner.

5.4.10.2. Stability studies

A stability study will be performed for one batch of [^{18}F]NaF injection manufactured according to synthetic processes, and dispensed into sterile injection vials, simulating routine storage of the drug substance. The shelf life of the product cannot exceed 5 half-lives of the radionuclide; hence the stability study will be limited to 10 hours. [^{18}F]NaF injection content and any incidental impurities will be monitored by HPLC.

5.4.10.3. Results and conclusions

No formal results are available to date. From the day-to-day experience of using [^{18}F]fluoride in PET radiopharmaceutical production there is no evidence of any significant physical or chemical changes in [^{18}F]NaF injection, except for the expected radioactive decay. No significant changes were observed in appearance, [^{18}F]NaF injection content or radiochemical impurities.

[^{18}F]NaF injection should be stored at ambient temperatures not exceeding 30°C. It will be tested to its full specification prior to use. The drug substance is not isolated in the manufacture of batches of drug product, therefore all quality control tests will be performed on a final product.

5.5. DRUG PRODUCT

5.5.1. Description and composition of the drug product

Description

[^{18}F]NaF injection, is a physiologic saline solution filled in standard 10ml sterile glass vials, comprising a rubber stopper and aluminium crimp-cap and containing 1–10 GBq of [^{18}F]NaF (present as the sodium salt).

5.5.2. Composition

The complete statement of the components and quantitative composition of [^{18}F]NaF injection is given in table 5.5.

TABLE 5.5. COMPOSITION OF [^{18}F]NaF INJECTION

Component	Quantity		Function	Reference to standard
[^{18}F]NaF injection *	1.0 GBq	10.0 GBq	Active	
Sodium Chloride 0.9%	10 ml	10 ml	Solvent	Ph.Eur.
Total Fill Volume	10 ml		-	-

* The actual quantity of [^{18}F]NaF injection used may be adjusted based on the irradiation parameters of each batch.

5.5.3. Pharmaceutical development

This section is not relevant, as the drug product is simply a physiologic saline solution of the well-known radiopharmaceutical.

5.6. MANUFACTURE

5.6.1. Manufacturer(s)

The manufacture of [^{18}F]NaF injection is performed in accordance with GMP at the following facilities:

Company Name
Street address
Town
Country

5.6.2. Batch formula

For simple dosage forms it may not be necessary to include this information in the clinical trial authorization (CTA) at this stage of development.

5.6.3. Description of manufacturing process and process controls

The flow diagram of the manufacturing process of [^{18}F]NaF injection is given in figure 5.1.

5.7. IN-PROCESS CONTROLS

5.7.1. Controls of critical steps and intermediates

There is no control of critical steps and there are no intermediates. All quality assurance is achieved by process validation.

5.7.2. Process validation and/or evaluation

The process validation will be conducted according to the manufacturer's internal standard operating procedures (SOP) and quality assurance (QA) policy in full respect of GMP recommendations.

5.8. CONTROL OF EXCIPIENTS

5.8.1. Specifications

Not relevant, no excipients are used.

5.8.2. Excipients of human or animal origin

Not relevant, none involved.

5.8.3. Novel excipients

None involved.

5.9. CONTROL OF DRUG PRODUCT

5.9.1. Specification(s)

Clinical trial batches will meet the following specification at release.

TABLE 5.6. REGULATORY SPECIFICATION FOR [^{18}F]NaF INJECTION VIALS 1 TO 10 GBq

Test	Acceptance criteria
Description	A clear transparent solution contained in a 10 ml glass vial closed with a rubber septum and aluminium crimped cap
Identification of [^{18}F]NaF injection by HPLC	The retention time of the principal peak in the radioactivity detector trace of a sample chromatogram spiked with the reference standard compound corresponds to that of the principal peak in the conductivity detector trace of the same chromatogram
[^{18}F]NaF injection content by dose calibrator	90.0 – 110.0% of label claim
Radiochemical purity by HPLC	Greater than 98.5%
pH by pH-paper	5.-8.5
Endotoxin contamination by LAL test	Less than 17.5 IU/ml

5.9.2. Analytical procedures

The methods used to control the drug substance are summarised below. In the course of ongoing development, analytical methods will continue to be optimised, and revised methods will be implemented and appropriately validated.

5.9.3. Description of [^{18}F]NaF injection

- The solution is examined for conformance of colour and transparency. The contents are tipped out and examined against a white background;
- Contents of [^{18}F]NaF in [^{18}F]NaF injection by dose calibrator;
- Radioactivity assay is conducted in the validated and calibrated dose calibrator;
- Identification and Radiochemical Purity of [^{18}F]NaF in [^{18}F]NaF injection by HPLC;
- This method uses a Column Dionex Carbopac PA-100, 4x250mm and a Dionex Carbopac PA-100 Guard Column; injection loop: 20µL. Eluent is 100mM NaOH at a flow-rate 0.5 ml/min. Detection with radioactivity and conductivity detectors;
- This method is stability indicating and will detect any degradation products present.

5.9.4. pH of [^{18}F]NaF injection by pH paper

The pH of [^{18}F]NaF injection is determined using pH paper.

5.9.5. Bacterial endotoxin contents in [^{18}F]NaF injection by limulus amebocyte lysate

Bacterial endotoxin content is measured using the Endosafe Limulus Amebocyte Lysate (LAL) test system using the portable test system (PTS) kinetic reader from Charles River Company.

5.9.6. Validation of analytical procedures

At this early phase only brief details of the validation performed would be provided, but sufficient validation data would be in place to assure that the methods are suitable for use.

Identification and Radiochemical purity of [^{18}F]NaF in [^{18}F]NaF injection by HPLC. The method has been validated for specificity, linearity and repeatability.

5.9.7. Characterization of impurities

No information available yet, since no impurities were identified.

5.9.8. Justification of specification(s)

Batches will be released for clinical trial purposes only if the impurity profiles can be supported by available non-clinical data.

TABLE 5.7. BATCH ANALYSIS DATA FOR BATCHES OF [^{18}F]NaF INJECTION

Batch number		NaF-XXX
Input drug substance batch number		Same
Batch size (GBq)		1.361
Date of manufacture		DD/MM/YY
Site of manufacture		AAAAA
Use		Non-Clinical*
Test	Acceptance criteria	
Description	Clear transparent liquid contained in a 10 ml glass vials closed with a rubber septum and an aluminium crimp cap	Conforms
Identification	The retention time of the principal peak in the radioactivity detector trace of a sample chromatogram spiked with the reference standard compound corresponds to that of the principal peak in the conductivity detector trace of the same chromatogram	Conforms
[^{18}F]NaF injection	1-10 GBq of product	Conforms
Content	(90.0 – 110.0% of label claim)	
Radiochemical purity	More than 98.5%	Conforms
pH	5.5-8	Conforms

* Clinical batches will be manufactured on demand, as the shelf-life of the product is less than 10 hours.

5.9.9. Reference standards or materials

Reference standard of NaF was purchased from Fischer Chemical (Code: J/4548/06) Batch Number xxxxx.

5.9.10. Container closure system

The product is filled into 10 ml glass sterile vials closed with rubber septum and an aluminium crimp cap, packaged into the lead container for protection from ionising irradiation.

5.9.11. Stability

Stability studies will be conducted with testing for radiochemical purity and degradation products at regular intervals to confirm the stability of [^{18}F]NaF injection over the proposed shelf-life.

[^{18}F]NaF injection will be stored at temperatures not exceeding 30°C with a shelf life of 10 hours.

6. PART II PHARMACO-TOXICOLOGICAL DATA

6.1. PHARMACOLOGY

6.1.1. Summary

^{18}F-Sodium Fluoride ([^{18}F]NaF) injection is a selective bone-seeking imaging agent. Essentially all the ^{18}F-fluoride that is delivered to the bone through the blood is retained in the bone. Tracer retention by the bone is determined by the $^{18}F^-$ ion exchanges for an OH^- ion on the surface of the hydroxyapatite matrix of the bone.

Na^{18}F-PET has shown promise in the evaluation of skeletal metastases and there are no formal studies assessing its accuracy in patients with (condition) or comparing it to bone scintigraphy. A single case report of Na^{18}F-PET-CT imaging in a patient with metastatic renal carcinoma showed five lesions which were fluoride avid that were not seen on the CT [8] suggesting that this technique has potential in metastatic renal cancer.

6.1.2. Primary pharmacodynamics

After intravenous administration of [^{18}F]NaF injection essentially all the ^{18}F-fluoride that is delivered to the bone by the blood is retained in the bone. The $^{18}F^-$ ion exchanges for an OH^- ion on the surface of the hydroxyapatite matrix of the bone. In the second phase, the $^{18}F^-$ ion migrates into the crystalline matrix of the bone, where it is retained until the bone is remodelled.

There is no pharmacodynamic effects exerted by the [^{18}F]NaF injection as the radiopharmaceutical is manufactured in carrier-free conditions.

6.1.3. Secondary pharmacodynamics

Ionising radiation emitted by [^{18}F] presents an inherent risk factor and secondary effects due to the high absorbed irradiation.

6.2. SAFETY PHARMACOLOGY

6.2.1. History of Na^{18}F-PET imaging

Several decades before the introduction of PET, Na^{18}F was used as a radiopharmaceutical for skeletal imaging [9]. In the early 1990s, Na^{18}F was developed for PET imaging [10] and in the past decade, the clinical utility of the technique has been demonstrated in a number of studies. It has a number of desirable characteristics including rapid bone uptake and rapid blood clearance with images obtained within an hour of intravenous administration of the tracer [11]. No adverse effects were so far reported due to the use of [^{18}F]NaF injection in numerous studies across the globe.

Safety pharmacology studies were not conducted, as sodium fluoride is a well-known compound and is widely used as an additive to toothpastes to prevent caries.

Acute exposure to sodium fluoride may produce effects including nausea, vomiting, abdominal pain, diarrhoea, drowsiness, coma, convulsions, cardiac arrest, respiratory effects and death [12].

Maximum fluoride content is 4.52 mg per maximum patient's recommended dose [13].

The lethal dose of NaF to the average adult has been estimated to be between 32 to 64 mg fluoride/kg body weight. An acute dose of 5 mg fluoride/kg body weight has been considered minimum dose that might lead to adverse health effects [12]. Toxic Rat Dose: LD50 = 52mg/kg. Dosimetry of [^{18}F]NaF injection was published in ICRP 53 (Table 6.1).

TABLE 6.1. ESTIMATED ABSORBED RADIATION DOSE AFTER INTRAVENOUS ADMINISTRATION OF SODIUM FLUORIDE F-18 INJECTION IN HUMAN ADULTS (70 KG) [FDA, 2000]

Organ	**Estimated Radiation Dose mGy/MBq**
Adrenals	0.0062
Brain	0.0056
Breasts	0.0028
Gallbladder wall	0.0044
Lower large intestine wall	0.012
Small intestine	0.0066
Stomach	0.0038
Upper large intestine wall	0.0058
Heart wall	0.0039
Kidneys	0.019
Liver	0.0040
Lungs	0.0041
Muscle	0.0060
Ovaries	0.011
Pancreas	0.0048
Red marrow	0.028
Bone surfaces	0.060
Skin	0.004
Spleen	0.0042
Testes	0.0078
Thymus	0.0035
Thyroid	0.0044
Urinary bladder wall	0.25
Uterus	0.019
Effective dose equivalent	0.027 mSv/MBq

6.3. PHARMACOKINETICS

6.3.1. Summary

After intravenous administration of [^{18}F]NaF injection, ^{18}F-fluoride is rapidly cleared from the plasma in a bi-exponential manner. The first phase has a half-life of 0.4 hours, and the second phase has a half-life of 2.6 hours.

After administration of Na^{18}F-PET, it is rapidly cleared from the plasma in a bi-exponential manner with half-lives of 0.4 hours and 2.6 hours [14]. Almost all the Na^{18}F delivered to the bone is retained in a two-phase process [15]: first, the $^{18}F^-$ exchanges for an OH^- ion on the surface of the hydroxyapatite matrix of bone and this is followed by migration of the $^{18}F^-$ into the crystalline matrix of the bone where it is retained until the bone is remodelled [11].

Approximately 50% of the total injected Na^{18}F is taken up by the bone [11]. However Na^{18}F is rapidly cleared from the blood, one hour after administration of [^{18}F]labelled NaF, only about 10% of the injected dose remains in the blood [16]. No pharmacodynamic or kinetic drug interaction studies have been performed.

6.4. TOXICOLOGY

6.4.1. Summary

Studies with [^{18}F]NaF injection have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility. Animal reproduction studies have not been conducted with [^{18}F]NaF injection. In contrast, the toxicology of the non-radioactive compound is well established due to extensive use in municipal water fluoridation systems, various dental products, and in a variety of industrial applications [17, 18]. Approximately 75–90% of the fluoride ingested each day is absorbed from the alimentary tract [17]. The *in vitro* data indicates that the genotoxicity of fluoride is limited primarily to doses much higher than those to which humans are exposed to on a daily basis. In addition, genotoxic effects are not always observed, even at high doses, and the preponderance of the genotoxic effects that have been reported are of the types that probably are of no or negligible genetic significance [17]. Adverse effects on reproductive performance associated with high concentrations of fluoride intake have been reported in nonclinical studies; the water or food threshold fluoride concentration associated with these effects is approximately 100 mg/L (100 mg/kg) [17]. Two-year, dosed water studies found equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas in dosed animals [18]. There was no evidence of carcinogenic activity in female F344/N rats or in male or female B6C3F1 mice receiving sodium fluoride at concentrations of 25, 100 or 175 ppm for two years [18]. The large number of epidemiological studies in humans showing a lack of correlation of cancer risk with drinking fluoridated water suggests that if any link exists, it must be very weak [17].

The toxicology of [^{18}F]NaF injection will be the same as that of the non-radioactive compound, except for the radiation exposure. However, the amount of fluoride ions in [^{18}F]NaF injection at the indicated dose is very low, and provides assurance that toxic effects will not be observed.

6.4.2. Reproductive toxicology

No studies have been completed to date. Repeated dose studies are not relevant, as the product is a diagnostic imaging agent, only single injection will be administered for the purpose of this study.

6.4.3. Mutagenicity and genotoxicity

No studies conducted.

6.4.4. Discussion and conclusion

The pharmacological profile of [^{18}F]NaF injection is considered to support the proposed clinical trial(s). The pharmacokinetics are favourable and compatible with the timeframe of the PET imaging study.

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) recommends that the highest dose of [^{18}F]NaF injection should be limited to 370 MBq.

6.5. CLINICAL DATA

6.5.1. Introduction

This study, will assess the efficacy of [^{18}F]NaF injection in evaluating renal cell carcinoma skeletal metastases. It will determine if ^{18}F-labelled sodium fluoride PET-CT (Na^{18}F-PET-CT) is more sensitive at detecting bone metastases in renal cell carcinoma than conventional techniques i.e. planar bone scintigraphy and computed tomography (CT). It is a pilot study and 10–20 patients will be evaluated in the first instance.

The current techniques used for detecting bone metastases in advanced renal cell carcinoma have low sensitivity. A very high sensitivity is required in two groups of patients: those that are thought to have no metastases and will undergo curative resection and those that have a solitary bone metastasis that will undergo resection of both the primary and the solitary metastasis. In both these groups, knowledge of a second metastasis will alter patient management. We propose that an imaging test with a very high sensitivity for bone metastases will have a clinical role in these patients.

6.5.2. Role of [^{18}F]NaF injection in detection of bone metastases

There is evidence from other groups of patients with skeletal metastases that the use of [^{18}F]NaF injection with PET-CT has a higher sensitivity for detecting bone metastases than planar ^{99m}Tc-MDP bone scintigraphy. This has not been explored in patients with (condition) and this pilot study will address this question. Furthermore, Na^{18}F-PET-CT takes a shorter amount of time than conventional scintigraphy, provides an equivalent dose to the patient and may help to overcome the current supply problems that are being encountered with ^{99m}Tc-based agents.

6.5.3. Study objectives and endpoints

The primary objective is to determine if [^{18}F]NaF injection with PET-CT is more sensitive at detecting bone metastases in (condition) than conventional techniques i.e. planar bone scintigraphy and computed tomography (CT). Number, site, and extent of metastases will be evaluated. The primary endpoint is to detect and compare the number of metastases detected with Na^{18}F^{-}PET-CT, ^{99m}Tc-MDP bone scintigraphy and multidetector CT.

The secondary objectives are to compare the sensitivity of multidetector CT with bone scintigraphy for detecting bone metastases in (condition) and to assess whether $Na^{18}F$-PET and CT images can be used to predict or correlate response to treatment in (condition).

6.5.4. Trial design

This is a single centre feasibility study that will recruit NN patients in the first instance with known or suspected metastatic (condition) i.e. M1 disease. Patients with known bone metastases will have been detected with ^{99m}Tc-MDP bone scintigraphy or CT (which are routine investigations for patients with renal cell carcinoma (RCC)) or another imaging investigation e.g. plain film or magnetic resonance imaging (MRI). For the purpose of this study, bone metastases may be suspected if there is bone pain, a bone mass or neurological symptoms felt to be due to bone metastases. Where possible, all patients will be treatment-naïve. If within the first six months of the trial, insufficient patients (less than five) who are treatment-naïve can be recruited, then patients who have had a single cycle of treatment will also be recruited. If patients withdraw from the trial before the imaging investigations have been completed, then they will be replaced. After preliminary review of the first NN patients, a further NN patients may subsequently be recruited.

The patient will have an initial unenhanced high resolution CT from vertex to toes (including limbs) which is performed on the same machine as the PET study. This will be of higher resolution (and higher dose) than the usual attenuation-correction CT and is required for optimum identification of metastases on CT. Following this, the PET images will then be acquired from vertex to toes and this will take approximately 60 minutes. The patient will be injected intravenously with up to 250 MBq of [^{18}F]NaF injection prior to the PET acquisition.

A bone scintigraphy will be performed within 28 days prior to the PET-CT study. These patients will be injected with up to 600 MBq of ^{99m}Tc-MDP up to three hours prior to imaging. A bone scintigram will be acquired from vertex to toes and this takes approximately 30 minutes to perform.

Patients will have a contrast-enhanced CT of the thorax, abdomen and pelvis approximately three months after diagnosis which is part of standard of care for these patients. Patients will be followed-up to determine disease progression and/or response to treatment for up to one year. Follow-up will be determined from their routine clinical visits, medical records, discussion with the patient's clinician. A follow-up phone call may be required if the patient does not have a routine clinic visit and this will take place within two weeks of the last scan and will last approximately 15 minutes. The patient will be asked to give their consent for follow-up, and if they withdraw consent from the study, no further follow-up will be undertaken unless the patient has given their express consent to this.

6.5.5. Data analysis

All images will be anonymized and reviewed by a nuclear medicine physician or a radiologist. A different individual will review each of the following studies: (1) the $Na^{18}F$-PET study in conjunction with the CT, (2) the ^{99m}Tc-MDP bone scintigram and (3) the unenhanced CT. Each individual will label the location and extent of metastases on a plan of the skeleton to indicate their distribution and the three plans will be correlated to determine which test is the most sensitive. The PET images will be analysed by measuring the mean and maximum Standardized Uptake Values (SUV) within the metastases.

The patient will be informed about the results of the PET-CT and bone scintigraphy if they wish to be informed. For most patients, the detection of an extra bone metastasis will not change management. Occasionally, a bone metastasis detected with $Na^{18}F$-PET-CT may require specific treatment e.g. if there may be a risk of fracture. If the patient's oncologist

thinks that this may be the case, then where possible, a further imaging test will be used to confirm the presence of this metastasis e.g. X ray or MRI. In these cases, entry into the trial may change the treatment that the patient receives.

The data will also be used in an exploratory study to assess the relationship between vascular calcium levels, cardiovascular risk and accumulation of $Na^{18}F$. No extra imaging will be performed for this part of the study and the data acquired for the main study will simply be re-analysed. The only additional information required will be a request from the patient during consent to assess their cardiovascular risk from their notes/history. Vascular calcium scores will be performed for the aorta, carotid, iliac and femoral arteries. SUVmax measurements will be performed on a slice-by-slice basis. Vascular calcification will be correlated with areas of $Na^{18}F$ uptake and, if available, this will be related to cardiovascular risk. Given that the significance of these results is unknown, this information will not be disclosed to the patient or the patient's clinician.

APPENDIX I. **TERMINOLOGY**

I.1. RADIOPHARMACEUTICAL

For the scope of this document the term radiopharmaceutical refers to a diagnostic radiolabelled chemical or biological entity for use in PET or SPECT, which has already been used in human clinical trials; and has already shown diagnostic potential and medical usefulness.

I.2. RADIOCHEMICALS AND RADIOPHARMACEUTICALS

An understanding of the difference between radiochemicals and radiopharmaceuticals is essential. Preparations are regarded as radiochemicals but not as radiopharmaceuticals (USP <1015>) if:

(i) They are not prepared according to a validated process that provides a high degree of assurance that the preparation meets all established requirements for quality and purity.

(ii) They have not been certified by qualified personnel (licensed pharmacists, approved physicians or other certified professionals) in accordance with published pharmacopeial methods.

Both radiochemicals and radiopharmaceuticals preparation can be manufactured within the same facility.

I.3 REGULATORY REFERENCES AND DEFINITIONS

There are a number of national and international bodies that have been tasked with assuring that medicinal products for human use are of the required safety and quality. It is essential to have a good understanding of this regulatory framework before attempting to get a radiopharmaceutical approved for commercial or in-house use.

I.3.1. Good manufacturing practice

Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production. The main risks are: unexpected contamination of products, causing damage to health or even death; incorrect labels on containers, which could mean that patients receive the wrong medicine; insufficient or too much active ingredient, resulting in ineffective treatment or adverse effects. GMP covers all aspects of production; from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product. There must be systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process - every time a product is made. The World Health Organization (WHO) has established detailed guidelines for good manufacturing practice. Many countries have formulated their own requirements for GMP based on WHO GMP. Others have harmonized their requirements, for example in the Association of South-East Asian Nations (ASEAN), in the European Union and through the Pharmaceutical Inspection Convention.

I.3.2 Good clinical practice

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected and consistent with the principles based on the Declaration of Helsinki, and that the clinical trial data is credible.

I.3.3 Pharmacopoeia standard

There are several international pharmacopoeias (such as Ph. Int., Ph. Eur., Jap. Ph., USP etc.). The primary objective of pharmacopoeia is to introduce a standard regulatory framework for medicinal compounds with regards to their composition/quality and the testing thereof.

I.3.4 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry of Europe, Japan and the United States to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has evolved, through its ICH Global Cooperation Group, to respond to the increasingly global face of drug development, so that the benefits of international harmonization for better global health can be realized worldwide. ICH's mission is to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

I.3.5 Declaration of Helsinki

The World Medical Association’s (WMA) declaration of ethical principles for medical research involving human subjects.

I.3.6 Regulatory agencies

FDA, EMA, MHRA, MHLW etc. The competent authority responsible for authorizing, licensing or approving the production of the diagnostic agent for routine clinical use.

I.3.7 Magistral formula

Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient.

I.3.8 Officinal formula

Any medicinal product which is prepared in a pharmacy in accordance with the specifications of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question.

I.3.9 Investigational medical product / investigational new drug

Investigational medical product / investigational new drug (IMP/IND) is a pharmaceutical form of an active substance being tested in a clinical trial, including products already with a marketing authorization but used or assembled in a different way from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

I.4 CLINICAL TRIALS

Clinical trials (as per EMEA Committee for Proprietary Medicinal Products Efficacy Working Party CPMP/EWP/1119/98/Rev. 1, Jan 2010; adapted to diagnostic clinical imaging agents) phases are described as follows:

Phase I: To obtain pharmacokinetic and first-in-human safety assessments with single or increasing mass doses of a diagnostic agent. Pharmacokinetic data enables the calculation of human dosimetry. This phase, and the subsequent Phase II, is designed to optimize the administered activity in order to reduce the patient radiation dose to as low as reasonably achievable (ALARA principle), whilst still providing high quality imaging.

Phase II (dose-response): Establishment of the dosing regimen to be used in Phase III studies. It provides preliminary evidence of efficacy and safety, indications and how to optimize the technique and timing of the imaging protocol (e.g. image acquisition or blood sampling). This phase aims at development of methods/criteria by which images and/or test results are processed and evaluated.

Phase III: Large-scale, multi-centres trials to establish efficacy of an investigational agent in a well-defined target patient population (e.g. in patients with suspected but not confirmed disease). The outcome of these trials usually defines how the test will be used in clinical practice.

Phase IV: Post marketing studies. Phase IV covers all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are intended to delineate additional information including the drug's risks, benefits, and optimal use.

I.5 LICENSED AND UN-LICENSED RADIOPHARMACEUTICALS

The scope of these recommendations is to cover all radiopharmaceuticals including licensed and un-licensed products as defined below:

— Licensed radiopharmaceuticals are those that are manufactured under GMP requirements and have a marketing authorization.

— Unlicensed radiopharmaceuticals are those that are manufactured under GMP conditions but without a marketing authorization, including:

- Magistral/extemporaneous preparations;
- Products manufactured and supplied from a licensed facility on a named patient basis;
- Officinal/stock preparations;
- Investigational medical products (IMP).

It is important to note that the same GMP requirements are required for both categories of products. In other words, the product administered to the patient must always meet the safety, purity and efficacy requirements. Also note that magistral preparation is allowed only in case the radiopharmaceutical is not available as licensed product with marketing authorization.

APPENDIX II. **EXAMPLES OF EXISTING STANDARDS**

The applicant has to be aware of the local regulatory requirements. These are some of the current standards that may be useful as a reference.

II.1 EUROPEAN UNION

In Europe, the manufacture and use of radiopharmaceuticals, both for clinical routine and for clinical studies, are regulated by several European bodies and by national authorities.

Directives (laws) on medicinal products are proposed and, once approved by the European Parliament and Council, are implemented by the European Commission-Directorate-General for Health and Consumers Regulation of Medicinal products for Human Use, with effect in all Member States. This administrative authority checks that each member country is applying EU law properly. Volume 4, Guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use, describes the rules for manufacturing medicinal products, including radiopharmaceuticals, whereas clinical trials are regulated by the general directives given in "The rules governing medicinal products in the European Union, Volume 10". Radiopharmaceuticals are manufactured following the rules described in Annex 3 of Volume 4. Additionally, because most of radiopharmaceuticals preparations are injected intravenously and not terminally autoclaved, the manufacture of sterile products has to be carried out in appropriate facilities as described in Annex 1 of Volume 4.

The European Medicine Agency (EMEA) is responsible for scientific evaluation of the quality, safety and efficacy of medicinal products that undergo an authorization procedure. This Agency is also responsible for maintaining and publishing the compilation of procedures on behalf of the European Commission. The specific additional information that needs to be submitted in relation to radiopharmaceuticals, in the context of applications for marketing authorizations, have been described in the Guidelines for radiopharmaceuticals (Ref. EMEA/CHMP/QWP/306970/2007).

The Council of Europe, European Directorate for the Quality of Medicines & HealthCare, establishes and provides official standards that apply to the manufacture and quality control of medicines in all signatory States of the "Convention on the Elaboration of a European Pharmacopoeia".

Beyond the regulatory bodies, the European Association of Nuclear Medicine (EANM) participates to the elaboration of clinical and pharmaceutical guidelines. This scientific association has recently edited a guideline entitled 'Current Good Radiopharmacy Practice' (CGRPP) in the preparation of radiopharmaceuticals manufacture of small-scale radiopharmaceuticals'.

Finally, the EU Commission, Directorate-General for Energy/Nuclear Energy is the European regulatory body responsible for protection against the dangers arising from exposure to ionizing radiation. This authority regulates production and handling of radiopharmaceuticals.

II.2 JAPAN

There are two types of radiopharmaceuticals in clinical usage, namely approved radiopharmaceuticals and compounded radiopharmaceuticals produced by approved synthesis modules. The Ministry of Health, Labour and Welfare (WHLW) and the Pharmaceutical and Medical Device Agency (PMDA) are responsible for the approval of radiopharmaceuticals and medical devices. For these radiopharmaceuticals GMP, GCP and good laboratory practice (GLP) are required in the production and delivery processes, pre-clinical safety testing and

clinical trials, respectively. Radiopharmaceuticals should be produced using an approved synthesis module and all the process and quality assurance should be done according to the guidelines and monographs published by a scientific organization (Japanese Society of Nuclear Medicine (JSNM)).

Recently, the JSNM Molecular Imaging Strategic Committee (JSNM-MISC) published "New Guidelines and qualification for research using in-house PET drugs", including a guideline for the standardization and quality assurance of in-house PET drugs; guidelines for standardization and quality control of PET imaging; guidelines for the clinical evaluation of PET drugs and guidelines for pre-clinical safety tests of PET drugs. JSNM-MISC is also working on developing and publishing new radiopharmaceuticals monographs. This is to facilitate safe and effective clinical research, as well as approval of synthesis modules for new radiopharmaceuticals. JSNM-MISC and National Institute of Radiological Sciences have started an educational program for PET radiopharmaceuticals production under the JSNM-Guidelines that operates site-visit programs for audit, and closely communicates with government authorities to harmonize the guidelines and government regulations.

II.3 UNITED STATES OF AMERICA

The current standard for the manufacture of PET radiopharmaceuticals ('drugs') in the United States is 21 CFR 212. This standard applies to approved PET radiopharmaceuticals as well as PET radiopharmaceuticals in phase III and IV clinical trials. PET radiopharmaceuticals being produced for earlier phase clinical trials have the option to be produced using either the standards within 21 CFR 212 or chapter <823> of the United States Pharmacopeia (USP, 32nd edition, 2009). When choosing the USP option, there are many other USP chapters that are also relevant, including chapters on sterility (<71>), bacterial endotoxins (<85>), chromatography (<621>) and radioactivity (<821>).

The compounding of SPECT radiopharmaceuticals is governed by USP chapter <797>, as is the dispensing of both PET and SPECT radiopharmaceuticals.

There are three different regulations applicable to clinical trials involving drugs. 21 CFR 56 provides the regulations for Institutional Review Boards, which are local ethics committees that review all clinical research studies. 21 CFR 361 provides the regulations for radioactive drug research committees (RDRC), a local committee that is allowed to approve initial phases of clinical trials under certain conditions. 21 CFR 312 provides the regulations for Investigational New Drug applications, under which all clinical trials (other than RDRC) are performed.

II.4 AUSTRALIA

All medicinal products including radiopharmaceuticals should comply with documents by the therapeutic goods administration (TGA) referred to in directive 2001/83/EC, as amended. This guideline provides information about specific requirements for radiopharmaceuticals including an Australian Registry for Therapeutic Goods (ARTG) number for individual drugs and satisfactory licensing requirement for commercial operators to supply radiopharmaceuticals for clinical use. It applies to SPECT and PET radiopharmaceuticals manufactured and supplied by a commercial supplier. Radiopharmaceuticals that do not have ARTG number may be supplied by a commercial provider under the special access scheme (SAS) from TGA for a specific patient study.

A new radiopharmaceutical manufactured by an institution and used within its institution is usually exempt from licensing by TGA. It is controlled by the Institutional Review Board (IRB), which is usually the local area human ethics committee and local drugs ethics committees. The guidelines insist that the radiopharmaceutical may be prepared to

comply with the GLP standard than GMP, provided the preparation process complies with the quality control and validation process in accordance with the United States pharmacopoeia or British pharmacopoeia regulations and the synthesis modules used in the process are approved.

APPENDIX III. **EXAMPLES OF CLINICAL TRIALS**

III.1 CLINICAL TRIALS WITH CLINICAL MOLECULAR IMAGING AGENTS IN FRANCE

In France, clinical trials are conducted in accordance with the European Directive 2001/20/EC on the conduct of clinical trials, implemented in the national Health Code since 2006. For the authorization for the first administration to humans (exploratory and Phase I studies), and to the subsequent clinical phases (Phase II and Phase III) of a new clinical molecular imaging agent the following documents have to be provided:

III.1.1 An administrative dossier

This dossier consists of a *clinical trial authorization* form (CTA), which is common to all European countries. The study will be unambiguously identified by a unique EudraCT number, obtained from the EudraCT Community Clinical Trial System.

The sponsor (if applicable) should also provide evidence of the establishment of an insurance to indemnify the investigator/the institution against claims arising from the trial.

III.1.2 A clinical trial dossier

This dossier informs the authorities and the Ethics Committee on the design of the clinical study, including statistical considerations on how specificity and sensitivity will be determined. Information sheet and consent certificate are also part of the dossier.

III.1.3 An investigational medicinal product dossier

The investigational medicinal product dossier (IMPD) includes summaries of information related to the quality, manufacture and control of the new clinical molecular imaging agent, data from non-clinical studies and from its clinical use.

Thereafter, the completed documentation has to be forwarded to the following institutions:

- The French National Agency for Public Health (ANSM);
- The Ethics Committee(s) (i.e. to each EC responsible of a given investigator's institution);
- The French Agency for Nuclear Safety (ASN).

Sending may be done in parallel. Authorization to start clinical trials is given by the ANSM, after collecting favourable advices from the other two institutions.

III.2 CLINICAL TRIALS IN THE UK

There are a large number of legislative documents that govern clinical trials at a European and national level. At European level these are also supported by a number of guidance documents that explain how organizations may comply with the required legislation. In general guidelines are not legally binding but as they effectively spell out how legal obligations may be set in a harmonized manner, organizations are expected to comply with them, unless they have justification for not doing so.

The International Conference on Harmonization's Topic E6 (R1) Guidance for Good Clinical Trial Practice (ICH GCP) [19] is not specifically mentioned in the United Kingdom legislation, however legislation includes the requirement to comply with GCP as outlined in

EEC/2005/28/. But if a trial is to be included as part of a marketing authorization application, it is expected that ICH GCP is complied with.

The key directive is 2001/20/EC and each member state has to adopt and publish national legislation and administrative processes necessary to comply with the directive. In the UK this was achieved through The Medicines for Clinical Human Use (Clinical Trials) regulations 2004 Statutory Instrument 1031 which sets out the process for regulatory and ethical review in order to obtain a Clinical Trial Authorization (CTA) and a favourable result from an ethics committee (REC or ECA). In addition, it sets out the requirements about how each trial must be conducted. This has been amended several times since 2004. In SI 2004/1031 the sponsor has specific responsibilities for the following:

— Authorization for clinical trials and ethics committee opinion;
— Conduct of the trial;
— Pharmacovigilance;
— Manufacture of API and IMP;
— Importation;
— Labelling;
— Testing and release;
— Trial data management;
— Investigators brochure.

Some of these responsibilities can be formally delegated, but ultimately the sponsor is responsible. The trial cannot start until an authorization has been granted (CTA) and a favourable REC received.

The first step in an application is to obtain a EudraCT number. This is a unique identifier which is required for all trials conducted with an investigational medicinal product in any EU Member State. It can only be obtained from the EudraCT pages of the EMEA website.

The second step is to apply to authority for a CTA. This application needs to include at minimum the following:

— Covering letter;
— CTA application form;
— Trial protocol that complies with ICH E6 (R1);
— Investigators Brochure (information to support the trial rationale and safe use of the IMP);
— Medicinal product dossier (content described in CHMP/QWP/185401/2004);
— Scientific advice;
— EMEA decision;
— Trial specific labelling;
— Proof of Payment;
— MA or MIA together with a QP declaration of compliance with GMP for each manufacturing site.

The clinical trial directive 2001/20/EC [20] requires a favourable opinion to be obtained from a Research Ethics Committee before any trial can commence. The United Kingdom Ethics Committee Authority (UKECA) consists of:

— England (Secretary of State for Health);
— Wales (National Assembly for Wales);
— Scotland (Scottish Ministers);
— Northern Ireland (Department of Health, Social Services and Public Safety).

The application must be made by the chief investigator for the trial using the online application at www.myresearchproject.org.uk. The application considers the following:

- Complex ethical issues;
- Subject information and consent forms;
- Adults lacking capacity;
- Minors;
- Radiation;
- Insurance;
- Sponsors outside EU.

The applicant receives an acknowledgment letter providing approval of the trial unless an objection is raised by MHRA within 14 days.

III.3 CLINICAL TRIALS IN THE USA

The United States Food and Drug Administration (FDA) requires all clinical trials that involve drugs to be performed under an Investigational New Drug (IND) or exploratory Investigational New Drug (eIND) application. 21 CFR 312 covers all of the regulations governing IND applications. In short, the application must include the following:

- Cover Sheet;
- Form FDA 1571;
- Table of Contents;
- Introductory Statement and General Investigational Plan;
- Investigator Brochure;
- Protocol(s);
- References to Other Sources (INDs, drug master files, etc.);
- Introduction;
- Detailed information about the drug substance, including manufacturing information, stability and validation of the manufacturing process;
- Detailed information about the drug product, including manufacturing information, stability and validation of the manufacturing process;
- Placebo description (if applicable);
- Labelling;
- Environmental Impact;
- Pharmacology and Toxicology Information;
- Responsible Person(s);
- GLP Compliance Certification;
- Pharmacology and Drug Distribution;
- Toxicology: Integrated Summary;
- Toxicology: Full Data Tabulation;
- Previous Human Experience.

This information is required for all phases of clinical trials, though it is acceptable to obtain letters of cross-reference from the holders of other INDs using the same drug product (i.e. referencing another IND holder's pharmacology and toxicology data so that these studies do not have to be replicated).

An investigator is allowed to proceed with the clinical trial 30 days after the US FDA has received the IND unless the FDA responds to the IND and places a clinical hold on the trial.

The FDA will then release the clinical hold and allow the trial to proceed once the issues have been satisfactorily addressed.

A New Drug Application (NDA) can be submitted once enough data have been generated to support bringing the drug to market. The regulations are found in 21 CFR 314. In short, the application must include the following:

- Cover Sheet;
- Form FDA 356h (application form);
- Table of Contents;
- Summary of Application, including indications and intended use of drug;
- Chemistry, Manufacturing and Controls (CMC) Section;
- Nonclinical Pharmacology and Toxicology Section;
- Human Pharmacokinetics and Bioavailability Section;
- Microbiology Section (if required);
- Clinical Data Section;
- Statistical Evaluation of Clinical Data;
- Case Report Forms and Tabulations;
- Labelling;
- Patent Information.

Once the NDA has been approved, physicians are free to prescribe the drug. The drug may be used off-label for anything other than the approved indications. However, a clinical trial with an approved IND must be used to generate data to support a new indication.

TABLE III.1 ANALYTICAL PARAMETERS AND TEST METHODS TO RELEASE A RADIOPHARMACEUTICAL

TEST or PARAMETER	EQUIPMENT or METHODS
Identity of radionuclide	Ionisation chamber (Half-life), Gammaspectrometer/-spectrometry
Identity of radiopharmaceutical	Radio-HPLC/UPLC, Radio-TLC
Identity of drug substance	HPLC/UPLC, TLC
Radiochemical purity	Radio-HPLC/UPLC, Radio-TLC
Radionuclidic purity	Gammaspectrometer/-spectrometry Ionisation chamber (Half-life),
Chemical Purity	HPLC/UPLC, TLC, UV/Vis
Residual solvents	GC
Pharmaceutical or physiological parameters	pH, Osmolality
Microbiological parameters	LAL Test, Test of Sterility
Activity Content	Concentration Ionisation chamber
Specific Radioactivity	HPLC/UPLC and Ionisation chamber
Enantiomeric excess	Chiral HPLC/UPLC

APPENDIX IV. **EXAMPLE OF A PRODUCT SPECIFICATION FILE**

IV.1 PRODUCT SPECIFICATION FILE FOR [^{18}F]SODIUM FLUORIDE ([^{18}F]NaF)

(*Manufacturer*)   Clinical Trial No: EudraCT No: *Contract Giver*: Technical Agreement:

Type of Study	**[^{18}F]Fluoride PET-CT for detecting (condition)**		
Number of Patients :			
Recruitment Period :			
Name of Investigator (s)			
Name of Sponsor (s)			
Ethics Committee approval			
Name of Ethics Committee			
Unit/Department where study to take place			
CTA approval			

Investigation medicinal product details:

Product Name	**[^{18}F]NaF injection**
Form:	Liquid for injection
Strength: MBq/mL	Minimum 300 MBq in 10 mL calibrated to the time of injection
Pack Size:	10mL vial in lead container
Route of Administration:	Intravenous injection

Checked by (QP for manufacturer):..... Date:.....

Checked by (contract giver): ..... Date:.....

TABLE IV.1. [^{18}F]NaF SPECIFICATIONS

Criteria	Value	Method of control and frequency
Appearance of product solution	Clear, colourless solution free from particulates	Visual, every batch
pH	5.0 – 8.5	pH paper, every batch
Injected dose, MBq	*defined by contract giver,* MBq	Dose calibrator, each dose
minimum activity at time of injection	*defined by contract giver,* MBq	Dose calibrator
Volume	≤ 10 mL	Defined by chemical amount of impurities, every batch
Radiochemical purity	≥ 98.5%	Gamma detector response on HPLC chromatogram, every batch
Radiochemical identity	Retention time on HPLC corresponds to that of the reference standard.	Spike injection with the reference standard, every batch
Radionuclidic purity: • *Half-life*	110 ± 5 min	Dose calibrator, determined on validation batches
Chemical amount	NaF ≤ 4.52 mg/dose	UV detector on HPLC chromatogram, every batch
Radiochemical stability	> 10 hrs	Gamma detector on HPLC, validation batches
Chemical impurities:	no chemical synthesis is involved and no solvents are used	Not applicable
Endotoxins	LAL <17.5 EU/ml	Turbidimetric, PTS, every batch post-release

TABLE IV.2 FINAL FORMULATION

Ingredient	**Grade**	**Content in 10mL**	**Approved supplier**
Physiologic saline, 0.9%	Ph.Eur.	Up to 10 mL	

IV.1. **Ordering process**

For every batch the principal investigator or the authorized person designated by him must issue a prescription form to the PET/CT unit, stating the clinical trial number, date and scheduled time of injection, as well as all other relevant details.

The PET/CT unit will then raise the *research request form* to *manufacturer* with the CTA number and scheduled injection time and dose (template attached). This request form will be issued to the *manufacturer* requesting him to start the manufacturing of [^{18}F]NaF.

The lead-time from order to delivery should be at least one week in order to allow efficient planning of the cyclotron and radiopharmaceutical facility availability. In no case the lead-time can be inferior to two hours before the scheduled injection.

IV.2. **Outline of manufacture of active product and final formulation**

Radiochemistry facility of *manufacturer* is the manufacturing site of radiopharmaceuticals for PET and holds the Manufacturer's Authorisation (IMP) No for manufacture of Investigational Medicinal Products.

All the manufacturing activities at *manufacturer* are conducted in accordance with GMP as stated in EU Directive 2003/94/EC and in particular, Annex 13 Manufacture of Investigational Medicinal Products Vol. 4 [21], following the policies outlined in document *Site Master File* and detailed further in the quality assurance system through the corresponding standard operating procedures (SOP). The set of SOPs as well as the other relevant documents can be assessed on site.

Manufacture of all radiopharmaceuticals at *manufacturer* is based on aseptic processing in closed automatic devices with final sterilising filtration through the 0.22 μm filters. All the products are sterile injections formulated in physiologic saline or buffer solution.

The validation policy for every new radiopharmaceutical production process is described in SOP '*Validation of Radiopharmaceuticals'*.

The batch solution of the final product will be subjected to sterilizing filtration and aseptically filled into closed sterile injection vial (rubber septum and aluminum crimp-cap sealed vials).

Production of [^{18}F]NaF using the *model* radiochemistry modules (model = brand name) placed in the Hot Cell N.- of the *manufacturer* radiochemistry laboratory is described in detail in SOP No- (include name of the SOP).

[^{18}F]Fluoride is produced in a liquid target via the ^{18}O(p,n)^{18}F nuclear reaction using PET cyclotron by sending a beam of X MeV (X = energy of protons) protons onto [^{18}O]H_2O enriched water. The target water containing [^{18}F]fluoride is transferred into the *brand name* module where [^{18}F]fluoride is trapped on a conditioned Sep Pak Light QMA anion exchange cartridge. Metal impurities are eliminated on the QMA and washing the cartridge with water for injection. The [^{18}F]fluoride is eluted by passing 0.9% NaCl through the QMA cartridge and is transferred via a Cathivex-GS sterilising filter into the product vial where it is mixed with the desired volume of saline (added into the product vial through sterile product filter prior to the synthesis).

The final product is analysed before release using liquid chromatography (LC) with UV and radioactivity detection to determine chemical and radiochemical purity, following procedures described in SOP No QC of [^{18}F]NaF.

IV.3. **Starting materials**

The *manufacturer* policy on the primary materials handling is described in the SOP No Name, where the list of trusted suppliers can be found.

A freedom from TSE statement from major suppliers can be assessed in the primary material stock management documentation of *manufacturer*. There is no liable materials of animal origin used in manufacture or packaging of [^{18}F]NaF.

The reagents and consumables used for the manufacture of [^{18}F]NaF are listed in the table shown in III.2.

TABLE IV.3 REAGENTS AND CONSUMABLES FOR PRODUCTION OF [^{18}F]NaF

Item	Specification	Supplier / Catalogue No.	Storage
ABX Reagent Kit Water for injection vial, 750 uL Water for injection bag, 100 mL Sodium chloride syringe, 3 mL Syringe (sterile), 30mL Millipore Cathivex-GS filter	Pharmaceutical grade	ABX; K-6550TM K-6550TM-W1 K-6550TM-W2 K-6550TM-SI SVGS0250S	Store at RT
ABX Hardware Kit Cassette Sep-Pak Light QMA cartridge Conical Column reservoir, 10mL	Bioburden tested	ABX; K-6640TM 9180	Store at RT
Vygon tubing, 150 cm	Sterile	VYGON	Store at RT
Vygon tubing, 50 cm	Sterile	VYGON	Store at RT
11 mL or 25 mL Mallinckrodt Evacuated vial	Sterile	Covidien / DRN 4357 or DRN 4370	Store at RT
Vygon tubing, 15cm	Sterile	VYGON	Store at RT
Filter, Millex-GV	Sterile	Millipore (UK) LTD, SL GV 013SL	Store at RT
^{18}O Enriched water	Sterile	IsoChem	Store in a fridge at 2–8 °C
Male-male luer lock connector, Vygon	Sterile	Vygon 893.00	Store at RT
One way rotating valve	Sterile	Vygon 851.00	Store at RT
70% Ethanol solution, 2.5L	Ph.Helv.	Sigma Aldrich / 02877-2.5L	Store at RT
Needles	Sterile		Store at RT
Sterile swabs	Sterile		Store at RT
Klercide 70/30 - 70% Ethanol Spray	Sterile	Shield Medicare, KL1013	Store at RT

TABLE IV.4 DISPENSING/COLLECTION MATERIALS

Item	Quantity	Comment
Sterile Evacuated Product vial, 11 mL or 25 mL vials	2 or 3	Mallinckrodt
Extension tubing, 15cm	1 or 3	Vygon
Male-male luer lock connector	1 or 2	Vygon
One-way valve	1	
Air filter Millex GV	1	Millipore
Green needle, 0.80x50mm	3	
Blue needle, 0.60x25mm	1	
18mm Vent needle	1	Air Guard
Cathivex GS filter	1	Millipore, included in the reagent kit
70% Ethanol solution	20mL	Used for one transfer line cleaning
Extension tubing, 150cm	2	Dispensing line for BRAND NAME module
Extension tubing, 50cm	1	For use from the Line Sanitization Module

IV.4. **Packaging**

— Primary Container: Type 1 glass vial with rubber or silicone stopper and aluminium crimp cap (see table above for supplier).

— Secondary container: Lead container placed in a transport container with the locks.

Packaging and shipping will be done according to the SOP No Name:

- Swab tests will be made using alcohol wipes on the handle and lock to make sure no contamination has been transferred to the container. A clear result is when no activity is measured on the wipe above background levels;
- Surface dose rate will be measured and the container will be labelled with the correct hazard diamond;
- The radioactive material transport form will be complete and attached to the transport container;
- The carrier should also sign the form, as should the receiver;
- When the empty container is returned a copy of the completed consignment note should be received and filed in the consignment notes file in place of the original form.

IV.5. **Quality control testing**

The final product is not released for the injection before the QC procedures are conducted and the quality certificate is issued (SOP No Name). Sterility test procedures are performed on every production batch after the final release due to the short shelf-life of the products, not compatible with the time scale of the sterility test (SOP No Name).

The QC test procedures for [^{18}F]NaF will include identity, radiochemical and chemical purity assessment by means of LC with UV and gamma-ray detectors prior to release. The well-characterised reference standards will be used for these assays. Appearance and pH of the final formulation and bacterial endotoxines (LAL, SOP No Name) will be tested also prior to release. Sterility (filtration test, outsourced to the certified laboratory) and filter integrity test (bubble point, SOP No Name) will be performed on every production batch post-release after radioactive decay of the product.

The *manufacturer* will advise the *contract giver* of any unplanned deviations that occur which are not in compliance with agreed specifications. The *manufacturer* and the *contract giver* will agree any reworking of any out of specification product following the policies laid down in SOP No Name. Exception reports will be filed in the clinical trial folder.

Details of all analytical testing to be undertaken will be agreed with the QP and all results will be made available to the QP. Microbiological testing will form part of the post-release approval criteria.

IV.6. **Retained samples**

Due to the short half-life of the radioisotope incorporated into the final product and a limited production capacity there is no special retain sample produced. The *manufacturer* will retain any residual final product one year after the closure of the study. Retention samples will be kept in the *manufacturer* storage room in a designated cupboard and logged into the sample management system.

It should be noted that the final product has a short half-life due to radioactive decay and only non-radioactive impurities can be normally detected in the retention sample when more than 10 half-lives have passed after the end of production.

It is the responsibility of the *contract giver* to make provisions that any surplus product is returned to the *manufacturer*.

IV.7. **Product release and QP certification**

The *manufacturer* will release the product under special arrangements described in the SOP Release of radiopharmaceuticals for human PET produced under *manufacturers* IMP licence.

The *manufacturer* will provide a certificate of conformity for each batch of the product which will include the QP certification statement certifying that the product complies with the requirements of Article 13.3 of Directive 2001/20/EC. The QP will sign the post-release approval of the product batch documentation.

IV.8. **Stability, storage and labelling**

The product is a radiopharmaceutical containing ultra-short lived radionuclide ^{18}F with a half-life of 109.7 minutes. Therefore the shelf-life of the product is limited by the half-life of the isotope contained in the radiopharmaceutical and does not exceed 10 hours. The product will be stored in restricted access areas.

Shelf – life:	Stable more than 8 hours after the end of synthesis
Storage conditions:	Room temperature, in a lead-shielded secondary container
Source of information:	Stability tests at 8 hours EOS during validation
Labelling:	Standard manufacturer labels on the primary and secondary container: EXAMPLE OF A LABEL The clinical trial number will appear on the product release sheet.

IV.9. **Supply and transport of finished product**

The *manufacturer* will supply the product as directed in writing by the *contract giver* when the process is complete and QP authorization has been issued.

Product will be shipped under ambient temperature in a lead-shielded container. The shipped product container will be accompanied by the transfer sheet, which must be signed by the principal investigator or the person designated by him upon receipt of the product and returned to the *manufacturer*.

IV.10. Surplus and disposal of rejected product

The surplus of the product will be kept at *manufacturer* as a retained sample (see above). It is the responsibility of the *contract giver* to assure that any surplus is returned to the *manufacturer*.

The rejected product will be left in a lead-shielded container in a controlled area until decay (not less than 10 half-lives of the radionuclide). After which period it can be disposed of as a normal waste liquid after appropriate control of the residual radioactivity. No disposal into waste is allowed before decay. It is the responsibility of the PET/CT unit to make provisions for eventual disposal of the rejected product.

IV.11. Complaints and defect reports

The *manufacturer* will investigate all complaints within a reasonable time scale upon written request and will provide the *contract giver* with a written report. In the case of a potentially serious complaint the *manufacturer* will make an initial response within 24 hours.

IV.12. Pharmacovigilance

The *manufacturer* will advise the *contract giver* of any suspected adverse events that are reported to them at any time. It is the responsibility of the *contract giver* to report any important suspected adverse event related to [^{18}F]NaF injection.

IV.13. Product recall

The *manufacturer* has the responsibility to initiate a product recall. The *contract giver* will provide all necessary information quickly and accurately in order to assist in the recall.

IV.14. Archiving

All batch production documentation will be reviewed by the Head of QC and the final post-release approval of the QP will be obtained before archiving. Archives of the production documentation will be kept according to SOP No Name and will be stored for at least five years after the closure of the clinical trial.

Manufacturer contact details:

Name:	Job title: Director
Address:	Email:
	Tel:
	Fax:

Name:	Job title: Production Manager
Address:	Email:
	Tel:
	Fax:

Name:	Job title: Head of QC
Address:	Email:
	Tel:
	Fax:

Contract giver contact details:

Name:	Job title:
Address:	Email:
	Tel:
	Fax:

Name:	Job title:
Address:	Email:
	Tel:
	Fax:

Name:	Job title:
Address:	Email:
	Tel:
	Fax:

Product specification file approval:

Name: Signature: ***On behalf of the contract giver***	
Date:	Job Title:

Name: Signature: ***On behalf of the manufacturer***	
Date:	Job Title: Head of Quality Control / Qualified Person

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ACRONYMS AND ABBREVIATIONS

ALARA	As low as reasonably achievable
ANSM	French national agency for public health
API	Active pharmaceutical ingredient
ARTG	Australian Registry for Therapeutic Goods
ASEAN	Association of South East Asian Nations
AST	French agency for nuclear safety
ATSM	Diacetyl-bis (N4-methylthiosemicarbazone)
CGRPP	Current good radiopharmacy practice
CT	Computed tomography
CTA	Clinical trial authorization
DOTANOC	Somatostatin receptor PET tracers such as [(68)Ga-DOTA,1-Nal(3)]- octreotide
DOTATATE	Somatostatin receptor PET tracers such as [(68)Ga-DOTA,Tyr(3)]-octreotate (68)Ga-DOTATATE
DOTATOC	(DOTA0-Phel-Tyr3) octreotide (Ga-68 DOTATOC)
EANM	European Association of Nuclear Medicine
ECA	Ethics committee approval
EMEA	European Medicines Agency
FDA	US Food and Drug Administration
FDG	^{18}F-Fluorodoexiglucose
^{18}F-Choline	Fluorocholine
^{18}F-DOPA	Fluorodopa
^{18}F-FAZA	Fluoroazomycin arabinoside
^{18}F-FET	Fluoro-ethyl-tyrosine
^{18}F-FHDT	16beta-18F-fluoro-5alpha-dihydrotestosterone
^{18}F-FLT	Fluorothymidine
^{18}F-FMISO	Fluoromisonidazole
^{18}F-NaF	F-Sodium Fluoride
GBq	Gigabecquerel
GC	Gas chromatograph
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonization
ICRP	Radiation dose to patients from radiopharmaceuticals
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
IND	Investigational new drug
IRB	Institutional Review Board
JSNM	Japanese Society of Nuclear Medicine
LAL test	Limulus amebocyte lysate assay
LC	Liquid chromatography
MA	Manufacturing authorization
MDP	Methyl-dyphosphonate

MeV	Mega electron volt
mGy/MBq	Miligrays/Megabecquerels
MHLW	Ministry of Health, Labour and Welfare, Japan
MHRA	Medicines and Healthcare Products Regulatory Agency, UK
MIA	Manufacturing and importation authorization
MR	Magnetic resonance
MRI	Magnetic resonance imaging
mSv/MBq	Milisievers/Megabecquerels
NDA	New drug application
PET	Positron emission tomography
PET/CT	Positron emission tomography/computed tomography
Ph.	Pharmacopoeias
PSA	Prostate specific antigen
PSF	Product specification file
PTS	Portable test system
QA	Quality assurance
QC	Quality control
QP	Qualified person
Radio-TLC	Radio-thin layer chromatography
RCC	Renal cell carcinoma
REC	Research ethics committee
SOP	Standard operating procedures
SPECT	Single photon emission computed tomography
SUV	Standardized uptake value
TGA	Therapeutic Goods Administration, Australia
UPLC	Ultra performance liquid chromatography
USP	United States Pharmacopeia
UV	Ultraviolet
WHO	World Health Organization
WMA	World Medical Association
µA	Micro-amperes

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