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GUIDELINES

EANM guideline for the preparation of an Investigational Medicinal Product Dossier (IMPD)

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Abstract The preparation of an Investigational Medicinal Product Dossier (IMPD) for a radiopharmaceutical to be used in a clinical trial is a challenging proposition for radiopharmaceutical scientists working in small-scale radiopharmacies. In addition to the vast quantity of information to be assembled, the structure of a standard IMPD is not well suited to the special characteristics of radiopharmaceuticals. This guideline aims to take radiopharmaceutical scientists through the practicalities of preparing an IMPD, in particular giving advice where the standard format is not suitable. Examples of generic IMPDs for three classes of radiopharmaceuticals are given: a small molecule, a kit-based diagnostic test and a therapeutic radiopharmaceutical.

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Introduction

The present document has been prepared with the aim of providing the radiopharmacy/radiochemistry community with a guideline to assist in the preparation of Investigational Medicinal Product Dossiers (IMPD).

In Europe, radiopharmaceuticals are considered as a special group of medicines and their preparation and use are regulated by a number of European Union (EU) directives, regulations and rules that have been adopted by Member States. Some radiopharmaceuticals are prepared within a marketing authorisation (MA) track, although many are not registered products. Small-scale preparations in non-commercial sites [hospital pharmacies, nuclear medicine departments, positron emission tomography (PET) centres] indeed represent an increasingly important segment of the market. The "Guidelines on Good Radiopharmacy Practice" [1] and "Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals" [2], issued by the Radiopharmacy Committee of the European Association of Nuclear Medicine, are useful references for quality assurance in the small-scale preparation of radiopharmaceuticals and their non-radioactive precursors. In-house prepared radiopharmaceuticals may be used for routine clinical (diagnostic or therapeutic) purposes or to investigate disease-related physiological functions. However, when it comes to use of radiopharmaceuticals in clinical trials, the EU produced a specific legislative framework, with the 2001/20/EC Directive, which defines a general "road map" to be considered by the applicant [3]. This Directive will be replaced in 2016 by a new Regulation, as recently issued by the European Parliament [4].

However, at the time of release of the present guideline, the Directive 2001/20/EC is still in force and will be taken as the reference. Moreover, the new Regulation will not eliminate the need to prepare an IMPD as part of the clinical trial application process. Directive 2001/20/EC imposed severe constraints on small-scale radiopharmacies, making clinical trial applications a challenging task. The most critical points may be summarised as follows:

1. Requirements for large clinical trials conducted by pharmaceutical companies are virtually the same as for small academic units in hospitals or at universities.
2. Some radiopharmaceuticals have monographs in the European Pharmacopoeia (Ph. Eur.) but few are registered products. Thus, in many instances a radiopharmaceutical will be considered as an IMP, even if its efficacy and safety have been demonstrated in clinical use over many years (e.g. [^{11}C]choline, [^{18}F]fluoroethylcholine, [^{11}C]PIB, etc.).
3. It should be stressed that, based on risk assessment analysis and due to the extremely small injected quantity, radiopharmaceuticals have an excellent safety profile.
4. Another major problem with the Directive is the need for good manufacturing practice (GMP) compliance in the preparation of investigational radiopharmaceuticals. In general, the logistics (e.g. size of the facility, number of available radiochemistry units), personnel and financial resources in a typical PET centre or nuclear medicine department make it very difficult and expensive to fully comply with GMP, especially considering that often the clinical trials are conducted on a relatively small number of patients.
5. Last but not least, clinical trials under the umbrella of Directive 2001/20/EC and subsequent guidelines require the preparation of an enormous amount of specific documentation, a significant part of which is represented by the IMPD. Thus, it becomes clear how the position of European research institutions in the field of molecular imaging with radiopharmaceuticals may be endangered by the sum of the above factors.

The new EU Clinical Trials Regulation introduces significant changes for radiopharmaceuticals [4]. First of all, the legal form of the Regulation will ensure that all Member States base their assessment of an application for authorisation of a clinical trial on an identical text, thus eliminating the differences due to the broad range of approaches that may be typically encountered from country to country when a Directive has to be transposed into national law. This is particularly evident in the case of radiopharmaceutical legislation. Further, it recognises that there are clinical trials which pose a minimal risk to the subject safety, compared with normal clinical practice; in general, the concept of risk assessment is considered to play a significant role in evaluating safety concerns, and this may lead to a more pragmatic approach in the case of radiopharmaceuticals. Finally, in the new Regulation there are significant exemptions for diagnostic investigational radiopharmaceuticals related to the need for a qualified person and the holding of a specific authorisation, the amount of information to be stated on the label, etc.

The European Association of Nuclear Medicine (EANM) has provided a series of documents and guidelines with the aim of helping the radiopharmaceutical community to comply with EU legislation, and also to contribute to general debate and discussion about the above issues. In this context, the Radiopharmacy Committee of the EANM has prepared a guidance document on "Good Radiopharmaceutical Practice (cGRPP) for small-scale production of radiopharmaceuticals" [2] which aims to provide a more sustainable alternative to the classic GMP that applies to the pharmaceutical industry, while

ensuring the same quality, safety and efficacy standards. cGRPP should provide a general framework covering practical aspects of the small-scale preparation of PET, single photon emission computed tomography (SPECT) and therapeutic radiopharmaceuticals. On the other hand, the current EU Directive requires that radiopharmaceutical IMPs be prepared under full GMP compliance. Thus, cGRPP guidelines do not apply in this case, creating two different "tracks" depending on the final use of the radiopharmaceutical, even if the preparation is identical. It is the opinion of the EANM that cGRPP guidelines should also apply to the preparation of investigational radiopharmaceuticals and that there would be no reason to set any differentiation between radiopharmaceuticals prepared for in-house and clinical trial use; the instrumentation, environment, procedures, analytical methods, characterisation methods, etc. are in most cases the same, and no real distinction is required.

Despite the above considerations, the authorisation route for investigational radiopharmaceuticals requires the preparation of a detailed dossier, which should include all the necessary information related to chemical and pharmaceutical quality, as well as non-clinical data related to pharmacology, pharmacokinetics, dosimetry and toxicology, and of course a description of the clinical trial.

IMPD preparation is regulated by the European Medicines Agency (EMA) *"Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials"* [5]. The structure of the EMA guideline resembles that of the Common Technical Document (CTD) which is required for MA applications and comprises two main parts: the drug substance (the active pharmaceutical ingredient, or API) and the drug product (or finished product). These parts are further divided into subsections dedicated to detailed aspects such as structural information, batch analysis, analytical methods, etc. EMA guidelines provide concise suggestions with additional information for special classes of pharmaceuticals, such as herbal drugs or radiopharmaceuticals, taking into account their peculiar nature. With respect to the documentation required during a MA application, information included in the IMPD should particularly focus on the risk aspects, depending on the stage of the development of the particular (radio)pharmaceutical. Readers may also find it useful to consult additional guidance documents [6, 7].

As stated above, the present document has been prepared with the aim of providing the radiopharmacy/radiochemistry community with a guideline to assist radiopharmacies in the preparation of the chemical and pharmaceutical part of an IMPD, while non-clinical pharmacology and toxicology as well as previous clinical trials and human experience data will not be covered. The general structure and organisation outlined by the EMA guidelines will be followed, but the contents will be adapted in consideration of the special nature of radiopharmaceuticals, while keeping in mind the need to comply with general EU guidelines and principles. The information on the chemical and pharmaceutical quality is provided in two main sections, named (Drug substance) and (Investigational medicinal product under test). In many cases (this is true for most of the PET radiopharmaceuticals), the drug substance is not isolated and characterised during the radiopharmaceutical preparation process, especially when the process is continuous and automated; an example is represented by the information related to analytical procedures (methodology, instrumentation, validation) or batch release, which may only be defined for final drug product, whilst the "Drug substance" section is not applicable. For these reasons, in the proposed guidelines information in various "Drug substance" subsections is intentionally missing and the required details are indeed provided in the proper "Investigational medicinal product under test" subsections.

As examples of the approach described, generic IMPDs for [^{11}C]choline (Appendix 1), [^{68}Ga]DOTA-NOC (Appendix 2) and [^{177}Lu]DOTA-peptide (Appendix 3) are provided as electronic supplementary material. As previously mentioned, the competent authority should always be contacted to verify specific national requirements and regulations, if applicable.

Definitions

Guidelines are not mandatory but recommendations for the effective implementation of EU Directives by Member States.

Guidances are not mandatory but recommendations in a more specific and detailed form for the effective implementation of Directives by Member States.

Regulations are mandatory in all EU countries, being directly applied without translation into national legislation.

Directives are rules addressed by the EU Commission to Member States to be translated into the respective national legislation and effectively implemented. Directives are mandatory.

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

Small-scale radiopharmaceuticals (SSRP) are any in-house, small-scale prepared radiopharmaceuticals (for PET, SPECT or therapeutic applications), excluding preparations based on licensed labelling kits and generators, and also excluding preparation of kits.

Investigational radiopharmaceutical (IRP) for clinical trials refers to a radiopharmaceutical being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication or to gain further information about the authorised form.

Drug substance (synonyms: active pharmaceutical ingredient, API, active ingredient, medicinal substance) is any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body. Information on chemical precursors including those for synthesis of PET radiopharmaceuticals may be presented in a separate "Impurities" section. In many PET radiopharmaceutical preparation processes the drug substances are, as a rule, not isolated but remain in solution, giving advantages in handling and reducing the effect of radiolysis. For radiopharmaceutical kits, the active substance is considered to be that part of the formulation that is intended to permit binding of the radionuclide. In addition, the radiolabelled form obtained after radiolabelling with a suitable radionuclide should be described.

Drug product means a finished medicinal product which has undergone all stages of production, including packaging and excipients, purification and formulation, in its final container.

Excipient is any substance included in the finished product deliberately added with the aim of providing a suitable vehicle (e.g. 0.9 % NaCl solution) and/or to increase the stability of the final product (e.g. a free radical scavenger to limit autoradiolysis).

Preparation includes all operations of purchase of materials and products, production, quality control, release and storage of medicinal products and the related controls.

Starting material means any substance used in the preparation of a medicinal product, excluding packaging materials. Generally speaking, the term *precursor* includes each API starting material for the preparation of (radio)pharmaceuticals. A *precursor for radiolabelling* is any radionuclide produced for the radiolabelling of another substance prior to administration.

Substances for pharmaceutical use are any organic or inorganic substances that are used as active substances or excipients for the production of medicinal products. They may be used as such or as starting materials for subsequent formulation to prepare medicinal products.

Qualified person (QP) is a person with a relevant academic qualification who has several years experience working in pharmaceutical manufacturing operations and has passed examinations attesting to his or her knowledge [8]. The need for a QP has been extended to the preparation of IMPs for clinical trials since the introduction of EU Directive 2001/20/EC. In countries that are part of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), the same role may be termed responsible person (RP) or authorised person (AP).

Responsible person for the small-scale preparation of radiopharmaceuticals (RPR) is a person with an academic background equivalent to a QP, with at least 2 years of practical experience in radiopharmaceutical preparations, having shown sufficient scientific and technical education and experience in GRPP and related fields. The EANM syllabus on radiopharmacy [9] covers the main aspects of the necessary knowledge required for the professionals in radiopharmaceutical sciences. The RPR is ultimately responsible for all aspects of the preparation of radiopharmaceuticals, including investigational radiopharmaceuticals, at small-scale radiopharmacies including the release of these items, unless local or national regulations require different qualifications.

Small-scale radiopharmacy is a facility where the small-scale preparation of radiopharmaceuticals is carried out in accordance with national regulations. The term *small-scale* radiopharmacy is not related to the size of the facility, but only to the preparation of radiopharmaceuticals solely for in-house use.

Good Radiopharmaceutical Practice (GRPP) is described in the "Guidelines on Good Radiopharmacy Practice (GRPP)" issued by the Radiopharmacy Committee of EANM [1, 2].

Abbreviations

API	Active pharmaceutical ingredient
ART	Activity at reference time
CAS-RN	Chemical Abstracts Service registry number
cGRPP	Current Good Radiopharmaceutical Practice
CHMP	EMA Committee for Medicinal Products for Human Use
CoA	Certificate of Analysis
EANM	European Association of Nuclear Medicine
EMA	European Medicines Agency
GC	Gas chromatography
HPLC	High-performance liquid chromatography
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational medicinal product
IMPD	Investigational Medicinal Product Dossier
INN name	International nonproprietary name
IR	Infrared spectroscopy
IRP	Investigational radiopharmaceutical
IUPAC	International Union on Pure and Applied Chemistry
MA	Marketing authorisation
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
PET	Positron emission tomography

Ph. Eur.	European Pharmacopoeia
PIC/S	Pharmaceutical Inspection Co-operation Scheme
QC	Quality control
QP	Qualified person
RPR	Responsible person for the small-scale preparation of radiopharmaceuticals
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SPECT	Single photon emission computed tomography
SSRP	Small-scale in-house radiopharmaceutical
TLC	Thin-layer chromatography

Note: the italicised text available throughout the following document indicates direct quotes from the EMA (CHMP/QWP/185401/2004) guidelines [5].

Drug substance

The term "radioactive drug substance", or active substance, may have a different meaning, depending on the nature of the intended radiopharmaceutical. For instance, one document states "*for radiopharmaceutical kits, the drug substance, or active substance, is considered to be that part of the formulation that is intended to carry or bind the radionuclide or to permit its binding*", while "*in a radionuclide generator, both mother and daughter radionuclides are to be considered as active substances*" [10]. In general, the definitions given for radiopharmaceutical kits apply to most radiopharmaceutical preparations, as the drug substance is indeed to be considered as that part of the formulation which carries or binds the radionuclide. In most cases, due to the peculiar nature and transient existence of the radionuclide as well as for radioprotection requirements, radiopharmaceuticals are prepared following continuous processes, and the radioactive drug substances are not isolated, unlike during the preparation of typical non-radioactive pharmaceuticals. For this reason, during the preparation of IMPDs for radiopharmaceuticals it is sometimes difficult to follow the EMA format, and in these cases it is not possible to provide specific information related to the drug substance. Information on chemical precursors, including those to be used for synthesis of PET radiopharmaceuticals, may be presented in a separate "Impurities" section, if applicable (e.g. in the case of precursors prepared in-house). The chemical or biological precursor should be well characterised, and information on the preparation process, with special emphasis on chemical or biological impurities possibly generated during the preparation steps that may affect the subsequent use for radiolabelling and toxicology, should be provided and discussed. The above information may also be obtained from the precursor supplier.

Nomenclature

Information concerning the nomenclature of the drug substance [e.g. proposed INN name, pharmacopoeial name, chemical name (IUPAC, CAS-RN), laboratory code, other currently used names or codes, if any] should be given. *Where practicable, specific radioactivity, carrier free, non carrier added or carrier added status should be stated. For radionuclides, the isotope type should be stated*, following the IUPAC nomenclature [11]. *In the case of radionuclide generators or radionuclides obtained via a decay chain (e.g. radium-223), both parent radionuclide and daughter radionuclide are considered as drug substances. For kits, which are to be radiolabelled, the part of the formulation which will carry or bind the radionuclide should be stated, as well as the radiolabelled product. For organic chemical precursors, the same information should be provided as for drug substances* [5].

Structure

The structural formula should be given, if applicable. For small peptides, e.g. somatostatin analogues, the amino acid sequence should be indicated, together with the position of the radionuclide in the molecule. In the case of very high molecular weight macromolecules, such as proteins, the generic name (INN name, other currently used names) should be sufficient.

In addition to the above information, the molecular formula and molecular weight should be stated, if applicable. In the case of radiolabelled colloids, nanoparticles, antibodies or other molecules whose molecular weight or formula may not be precisely defined, a description of the components included in the radiopharmaceutical should be given (e.g. for a radiolabelled antibody, indications related to the selected antibody, the chelator moiety and the chosen radionuclide as well as the way they are conjugated and the estimated molecular weight of the final conjugate).

General properties

A list of physicochemical and other relevant properties of the active substance should be provided, in particular physicochemical properties that could affect pharmacological or toxicological safety, such as solubility, pKa, polymorphism, isomerism, log P, permeability etc. For radionuclides, the nuclear and physicochemical properties should be stated [5]. Often, the extremely low mass associated with a high specific activity radiopharmaceutical does not allow its full physicochemical characterisation, and the determination of parameters such as melting point, solubility or hygroscopicity

may not be directly applicable to radiopharmaceuticals. A second factor that hampers the characterisation of radiopharmaceuticals using standard methods is the need to protect operators from radiation burden. For instance, in radiolabelling a monoclonal antibody, the mass of the product would potentially be sufficient for MS analysis, but such a test could hardly be performed with a radiolabelled antibody. Thus, the list of physicochemical and other relevant properties presented in this section should refer to the "cold", non-radioactive counterpart of the radiopharmaceutical, rather than to the active substance itself (e.g. [^{19}F]FDG for [^{18}F]FDG). It should be noted that some of the above properties (e.g. melting point) are only indicative of the general characteristics of the active substance, but they are not relevant for the considered radiopharmaceutical, as the latter is typically present in tracer amounts.

If the mass quantity of the radiopharmaceutical is low, pharmacological and toxicological safety could be of no concern. However, the possibility that the specific activity obtained in practice could be lower than expected should always be considered. Further, radiopharmaceuticals might have a significant associated mass for other reasons (e.g. labelled nanoparticles or a radiolabelled kit, where a considerable excess of the molecule that binds the radionuclide is usually present in the final formulation). In such cases the physicochemical properties of the cold compound or unbound precursor should be indicated. For characterisation of macromolecules, UV spectra, gel electrophoresis and size exclusion, HPLC profiles are generally considered sufficient. Finally, the nuclear properties (e.g. nuclear reaction, decay mode, decay energy) of the intended radionuclides should be stated.

Manufacturer(s)

The name(s), address(es) and responsibilities of all the small-scale radiopharmaceutical preparation institutions and each proposed preparation site involved in the small-scale preparation and testing of an IRP should be provided in this section. If the drug substance is not isolated during the preparation process (e.g. in the case of PET radiopharmaceuticals), the above information may be reported in the "Manufacturer(s)" section.

Description of manufacturing process and process controls

For chemical substances: any relevant process controls should be indicated. Where critical steps in the synthesis have been identified, a more detailed description may be appropriate [5]. If the radionuclides are produced on-site (e.g. short-lived cyclotron produced radionuclides), the nuclear reactions should be described, including possible side reactions yielding undesired contaminant radionuclides. Typical irradiation conditions should be given, together with a description of the target (material, shape, other technical characteristics, cleaning procedures) used for the radionuclide production. The preparation process of the IRPs should be described, including the radiosynthesis process, a flow chart of the successive steps including and defining the critical steps, the starting materials, intermediates, solvents, catalysts and key reagents used. If applicable, a brief description of the automated synthesis module should also be given. In the case of APIs of biological nature, the manufacturing process of the starting materials must include the flow chart of the production with the characterisation (viral and bacterial status) of the cells used for production, a flow chart of the biomolecule functionalisation and the techniques used for purification and controls.

The stereochemical properties of starting materials (e.g. the organic precursor) should be discussed, where applicable. For substances which comply with a monograph of the Ph. Eur., or the pharmacopoeia of an EU Member State, no further details are required. More information about preparation process and process controls are provided in "Description of manufacturing process and process controls" section.

Control of materials

Materials used in the manufacture of the investigational radiopharmaceuticals (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed, together with a brief summary of the quality and control of any attributes anticipated to be critical, for example, where control is required to limit an impurity in the investigational radiopharmaceuticals final preparation (e.g. chiral control, metal catalyst control or control of a precursor to a potential genotoxic impurity [5]). Materials should be of pharmaceutical grade whenever possible. However, a suitable Certificate of Analysis (CoA) may be sufficient where materials are well known (e.g. solvents typically used in organic chemistry such as acetonitrile or ethanol; simple, non-toxic and/or not predictive for potential toxic impurities materials, such as commercially available solid phase extraction cartridges, etc.) and their manufacturers are well established and their use in the preparation of radiopharmaceuticals is validated. If the starting materials are registered products with a marketing authorisation (e.g. water for injection, 0.9 % NaCl physiological saline, etc.), the relevant Summary of Product Characteristics (SmPC) might be considered appropriate. This information can be presented in tabular form, indicating material name, function, manufacturer and quality. In the case of generators or a radionuclide precursor with a long half-life, a complete description of their characteristics should be presented (radionuclidic purity, specific activity, non-radioactive metal contaminants, sterility of radioactive solutions, activity at calibration time and elution yield for generator).

Control of critical steps and intermediates

The preparation of radiopharmaceuticals such as those for use with PET is usually performed with a fully automated synthesis module and, for this reason, both the intermediate and the active substance are not, as a rule, isolated. This means that controls of critical steps and intermediates cannot be performed as it is done for standard pharmaceuticals. However, it is possible, through the synthesis module control software, to monitor critical parameters such as reaction temperatures and pressure, gas flow and radioactivity trends in critical steps. Control of critical steps is also not applicable in the case of kit-based preparations consisting of simple operations such as mixing the radionuclide with the kit components and a suitable diluent. In the case of preparation procedures where intermediates may be isolated, or "in-process" controls are applicable, critical steps in the radiosynthesis, tests and acceptance criteria for the intermediate controls should be briefly summarised. Details are usually included in the quality documentation (e.g. SOP, validation protocols, etc.).

Process validation and/or evaluation

See the "Process validation and/or evaluation" section.

Manufacturing process development

As stated above, the preparation of a radiopharmaceutical is usually a continuous process, and the active substance is, as a rule, not isolated. Thus, the manufacturing process development will be evaluated as a whole in the "Description of manufacturing process and process controls" section.

Characterisation

Elucidation of structure and other characteristics

The short or very short half-life of many important radionuclides and the extremely small chemical quantity of the radiopharmaceutical in the final drug preparation do not allow the direct characterisation of the active substance with standard chemical analysis techniques such as NMR, MS, IR or elemental analysis. For this reason, the elucidation of the structure is usually performed on the non-radioactive analogue of the desired radiopharmaceutical. Elucidation of the structure of the cold counterpart may not be necessary in the case of a commercially available reference standard, provided it has been adequately characterised by the supplier and a suitable CoA is available. The labelled active substance may then be identified by comparison with the above cold analogue standard. For instance, the identification test, which is considered as mandatory by most Ph. Eur. monographs, may be performed by comparing the retention time of the radiopharmaceutical with that of the cold standard by means of analytical techniques such as HPLC. If all the isotopes of the selected element are radioactive (e.g. this is true for elements such as astatine or technetium) and a cold analogue does not exist, reference could be made to an element possessing similar physicochemical properties (e.g. the reference for ^{211}At might be the stable isotope of iodine ^{127}I). Finally, in the case of a radiometal-containing radiopharmaceuticals, sometimes the cold metal complex is not available as reference standard. In this situation it is recommended to use the metal-free precursor as reference standard if this can be justified from results obtained from analytical characterisation and validation.

Impurities

Since the preparation of a radiopharmaceutical is often a continuous process, and the active substance is, as a rule, not isolated, impurities are usually evaluated in the finished drug product. However, a discussion of the potential impurities generated during the preparation process might also be presented in this section.

Impurities may arise from any of the steps involved in the preparation process, from the production of the radionuclide to the radiolabelling process, and also from the precursor or other reagents/solvents used. Impurities may be generated during the production of the radionuclide (e.g. PET radioisotopes) or if the radionuclide is obtained from a generator (e.g. ^{99}Mo/^{99m}Tc or ^{68}Ge/^{68}Ga). The operations involved in labelling the desired precursor may also lead to the formation of both radioactive and non-radioactive impurities; radiochemical and chemical purity thus have to be assessed. Impurities may also result from radioactive decay and/or chemical decomposition of the drug substance as well as from purification cartridges or the container used to collect the final product. A brief discussion of the potential radioactive and non-radioactive impurities, based on the knowledge of the entire preparation process, should be provided. Analytical methods and their validation will be described in the "Analytical procedures" and "Validation of analytical procedures" sections.

Control of the drug substance

Specification(s)

Since the preparation of many radiopharmaceuticals is a continuous process and the active substance is not isolated, the specifications and associated analytical test only apply to the finished drug product. Details on the analytical methods, their validation, the batch analysis and the justification of specifications will be provided in the appropriate "Investigational medicinal product under test" subsections.

Analytical procedures

For the reasons stated above, analytical procedures will be described for the drug product in the appropriate sections.

Validation of analytical procedures

For the reasons stated above, validation of analytical procedures will be described for the drug product in the appropriate sections.

Batch analyses

For the reasons stated above, batch analyses will be described for the drug product in the appropriate sections.

Justification of specification(s)

For the reasons stated above, justification of specification(s) will be described for the drug product in the appropriate sections.

Reference standards or materials

Two different kinds of standards should be described in this section. Firstly, radioactive sealed calibration sources, to be used for dose calibrator(s) or to calibrate gamma spectrometer(s). Reference sources used to calibrate the dose calibrator could include a single, suitable long-lived radionuclide (e.g. ^{137}Cs). For the calibration of NaI or HPGe or other suitable gamma spectrometer detectors, a "multi-nuclide" or "multi-gamma" (e.g. ^{152}Eu) source might be preferred. In this case, it is very important that the entire energy spectrum generated by the decay of the reference radionuclides covers the desired measurement energy range (typically, 0–2,000 keV). Composition and activity of the selected calibration sources at reference date (and time, where applicable) should be stated, and a suitable certificate of calibration should be obtained.

Secondly, non-radioactive standards of the desired radiopharmaceutical (e.g. [^{19}F]FDG as a reference standard for the preparation of [^{18}F]FDG). The reference standards should be of suitable quality and purity. In case of well-known reference standards, a CoA should be generally considered as sufficient. However, a retest of the standards (e.g. by analysing it with HPLC and/or melting point) with the aim of verifying the purity could be necessary (e.g. after long-term storage). An expiry date should also be stated, irrespective of whether it is assigned by the applicant or set by the supplier.

It has to be noted that in some circumstances, such as ^{99m}Tc-labelled products, a cold reference standard as defined above does not exist, as there are no stable isotopes of technetium in nature. In this case, the respective cold compound or the free ligand may serve as reference standard, provided that results obtained following analytical validation clearly allow radiopharmaceutical identification using the ligand alone.

Container closure system

For the reasons stated above, container closure system will be described for the drug product in the appropriate sections.

Stability

For the reasons stated above, stability will be described for the drug product in the appropriate sections.

Investigational medicinal product under test

Description and composition of the investigational medicinal product

The qualitative and quantitative composition of the IRP should be stated or tabulated and the function of each component should be stated. Radioactivity should preferably be reported in terms of radioactivity concentration. An indication of the container closure system could be given in this section, although a more detailed description has to be provided in the "Container closure system" section.

Pharmaceutical development

A brief description of the entire process, with special emphasis on the radiosynthetic pathway and formulation development, should be provided. The peculiar nature of radiopharmaceuticals labelled with short- or ultra-short-lived radionuclides should be underlined, with the aim of providing a rationale for the necessary variability in formulation specifications, such as activity at reference time (ART). ART is defined as the activity (preferably expressed as a radioactive concentration) of the finished product, calculated at a suitable reference time, and should be stated on the label. Although EU guidelines suggest that ART should be standardised for the intended radiopharmaceutical (e.g. 185 MBq/ml at 10.00 a.m.), this is not always practical with short-lived radionuclides, in which case the actual time should be used.

Manufacturing process development

See the "Pharmaceutical development" section.

Manufacture

Manufacturer(s)

The name(s), address(es) and responsibilities of all the small-scale radiopharmaceutical preparation institutions, and each proposed preparation site involved in the small-scale preparation and testing of IRPs, should be provided. This also applies when the radionuclides or radiopharmaceuticals are used in

phase I microdosing studies in humans to develop a non-radioactive medicinal product. The manufacturer of the radiopharmaceutical precursors should also be stated. Similarly, any contracted laboratories whose results are used to document the quality of the final product should be listed, such as microbiology laboratories and solvent analysis. If multiple manufacturers contribute to the manufacture of the IRP, their respective responsibilities need to be clearly stated.

Batch formula

The batch formula should include all the materials (e.g. precursor, solvents, reactants, vials, filters, purification components, etc.) which are relevant in the preparation of a single batch of the desired IRP. Reference to the required data may be found in the quality documentation and dedicated manufacturing SOPs. The batch size, to be intended as the number of the single units (e.g. vials) of the finished drug product, should be stated, though often a batch of a radiopharmaceutical is a single vial.

Description of manufacturing process and process controls

A flow chart of the successive steps, indicating the components used for each step and including any relevant in-process controls, should be provided. In addition, a description of the manufacturing process should be included. In this section, more emphasis should be placed on the purification and formulation aspects of the preparation.

In case of continuous, automated preparation procedures, in-process controls are necessarily limited to the monitoring of the critical parameters through the graphical control software interface. Where manual or semi-automated preparation procedures apply, critical steps in the synthesis should be identified, and a more detailed description of the test to be performed may be appropriate. Other controls may include verification of environmental and microbiological parameters, although they have to be considered as indirect process controls rather than in-process controls.

The cleaning and segregation processes for the radiopharmaceutical preparation and the organic chemical precursors should be stated. The production scale or range of batch sizes to be used in the clinical trial should be stated, although batches of IRP are often represented by a single vial.

Controls of critical steps and intermediates

Description of in-process controls and intermediates has already been given in the "Control of critical steps and intermediates" section. However, this section could include information on the supply of vials, the sterile filters used and the environment in which the final filling process is performed.

Process validation and/or evaluation

The preparation process of the investigational radiopharmaceutical should be validated by preparing and submitting to a full quality control program three independent consecutive batches of the finished product. The batches should be of the same size and should be prepared under the same operating conditions, by following the same methods, and using the same starting materials and in the same quantity as expected for the batches to be used in clinical trials. Starting activity used for validation batches should be adequate to obtain the desired final product activity, based on the actual knowledge of the process. Due to the short or very short half-life of the relevant radionuclides and to the inherent nature of the process, a range of radioactive concentrations may be accepted for the final product. There should be a table of release specifications and a table of results of the test batches demonstrating conformity with the release specifications.

Control of excipients

Specifications

Reference to Ph. Eur. should be indicated, if applicable. If the excipient meets Ph. Eur. criteria, only a verification of appearance, packaging integrity, expiry date and CoA should be considered as mandatory, and the following subsections dedicated to the description of analytical procedures and justification of specifications should not apply. In the case of novel excipients, or in case the excipients do not meet the Ph. Eur. criteria, the following subsections apply.

Analytical procedures

In cases where reference to a pharmacopoeial monograph listed under the "Specifications" *section cannot be made, the analytical methods used should be indicated* [5].

Validation of the analytical procedures

Not applicable.

Justification of specifications

Not applicable.

Novel excipients

For novel excipients, details should be given about their manufacturing process, characterisation and control in relation to product safety [5].

Control of the investigational medicinal product

Specifications

Each batch of the radiopharmaceutical must undergo quality control, with the aim of evaluating the chemical, radiochemical, radionuclidic and biological purity of the finished product. Specifications and acceptance criteria for the various tests should be given in tabulated form, while the justification for the specifications may be discussed in the next "Justification of specification(s)" section. It should also be specified which tests have to be performed before or after the release of the finished product. The Ph. Eur. monograph "Radiopharmaceutical preparations" may be used as a general reference to establish procedures and specifications (e.g. for identification or radionuclidic purity tests) [12].

Analytical procedures

The analytical procedures, as well as the experimental conditions established during the (radio)pharmaceutical development phase (e.g. in case of HPLC analysis: mobile phase composition, pump flow, injected volume and quantity, UV wavelength, column type, acquisition time, etc.), should be described for all tests included in the specifications. Detailed information related to the instrumentation (e.g. HPLC pumps, columns, detectors, injection system, gamma spectrometer detector, pH metre, etc.) are available and may be found in the dedicated quality system documentation (e.g. SOPs, protocols).

Validation of analytical procedures

General International Conference on Harmonisation (ICH) guidelines on validation of analytical procedures indicate which parameters should be considered for validation, and which acceptance criteria should apply [13]. Analytical methods used to control the quality of the finished products should be validated; the validation of the parameters (accuracy, specificity, linearity, repeatability, etc.) listed in the above ICH guidelines are not always applicable to radiopharmaceuticals. For instance, the validation of parameters that rely on quantitation of radioactivity, such as limit of quantitation (LOQ) or accuracy, may in some circumstances not be relevant in case of radio-HPLC or radio-TLC analyses, where the radiochemical purity is determined as a ratio between areas or counts, and no absolute quantitative measurement is required to be performed.

Batch analyses

Data related to representative IRP batches should be included, preferably in tabulated form. They should report information related to the number and batch size as well as information on the production site, methods of production, production data (e.g. radiolabelling yield, finished product activity, specific activity and radioactive concentration), quality control test performed and results, and their acceptance criteria. Data obtained by validation runs may also be used for this purpose.

Characterisation of impurities

The discussion of impurities has already been provided in the "Impurities" section, related to the active substance.

Justification of specification(s)

For IMPs in Phase I clinical trials, it should be sufficient to briefly justify the specifications and acceptance criteria for degradation products and any other parameters that may be relevant to the performance of the radiopharmaceuticals. Toxicological justification should be given, when appropriate [5]. The definition of the specifications for impurities should be based on a combination of sources, such as experimental data achieved during the (radio)pharmaceutical development phase, scientific literature, if applicable, and with the help of appropriate guidelines [14, 15]. A classification of the impurities (e.g. residual solvents, organic/inorganic), a rationale for the reporting for defining acceptance criteria, limits and thresholds, with calculation examples, are given. Often for PET radiopharmaceuticals there will be residual solvents from HPLC purification or elution from a formulation module; the maximum solvent content should be measured and justified. Finally, the Ph. Eur. monograph "Radiopharmaceutical preparations" may be used as a general reference to help in the definition and justification of specifications [12].

Reference standards or materials

Reference standards and materials have already been discussed in the "Reference standards or materials section".

Container closure system

The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the IMP in the clinical trial, should be stated [5]. Usually the immediate packaging for radiopharmaceuticals consists of a glass vial, Ph. Eur. type I or type II, sterile and pyrogen free, closed with a bromo- or chlorobutyl rubber stopper (Ph. Eur. conforming), sealed with an aluminum cap, while outer packaging is typically a lead container whose thickness is appropriate for the intended shielding purposes. *If the product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided. For dosage forms that have a higher potential for interaction between filling and*

container closure system (e.g. parenterals), more details may be needed [5]. No further tests than visual inspection are applicable for immediate and outer packaging, provided that suitable certificate of analysis and information about the vials and stopper manufacturer are available.

Stability

The goal of stability testing is to provide evidence on how the quality of a radiopharmaceutical varies with time and to establish a shelf life for the finished product under recommended storage conditions. During the entire shelf life, the radiopharmaceutical characteristics of purity have to meet the quality criteria discussed and defined in the previous sections. It has to be noted that stability evaluation is of increasing relevance as the half-life of the radionuclides and, in turn, the shelf life of the radiopharmaceuticals, increase. For radiopharmaceuticals labelled with short or very short half-life radionuclides, samples could be analysed at the end of preparation (T_0) and then at the proposed expiry time (T_1), while in case of longer proposed shelf life, more intermediate analysis check points should be considered. Thus, an expiry time and date for the radiopharmaceutical product should be established. For stability study purposes, three consecutive batches of the IRP should be prepared, starting from the maximum possible starting activity of the intended radionuclide, in order to obtain batches with the highest radioactive concentration that allow one to evaluate the effect of autoradiolysis of the active substance in the worst case conditions. For each batch of radiopharmaceuticals, the following information should be provided: batch number, preparation date, calibration time and radioactive concentration at calibration time. Acceptance criteria for each batch of radiopharmaceutical are those defined in the "Specifications" section. Only stability indicating parameters have to be determined at the appropriate time intervals for the entire proposed shelf-life. In general, stability indicating parameters are: appearance, pH, radiochemical purity. However, a careful evaluation of the process should always be made, in order to clearly define and select the parameters to be controlled during the stability study. The remaining parameters, which are not considered as stability indicating, need to be analysed only once per batch.

Disclaimer

This guideline summarises the views of the Radiopharmacy and Drug Development Committees of the EANM and reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken into context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions. The guidelines were brought to the attention of the National Societies of Nuclear Medicine.

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