Whitepaper

Radiopharmaceuticals – How to Register in EU?

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White paper

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Introduction Radiopharmaceuticals: General aspects

Radiopharmaceuticals are a specific type of medicinal products. When ready for use they contain one or more radionuclides (radio-isotopes). Radionuclides dissipate excess energy by spontaneously emitting radiation in the form of alpha, beta, positron and gamma rays. Radiopharmaceuticals make use of the radiation emitted by radioisotopes. They are used for therapeutic (destruction of diseased body cells) and diagnostic purposes (detection of radiation and transforming into images).

Diagnostic use (SPECT/PET): "Radioisotopes emitting penetrating gamma rays are used for diagnostic (imaging) where the radiation has to escape the body before being detected by a specific device (SPECT/PET cameras). Typically, the radiation emitted by isotope used for imaging vanishes completely after 1 day through radioactive decay and normal body excretion."

Therapeutic use: "Radioisotopes emitting short range particles (alpha or beta) are used for therapy due to their power to lose all their energy over a very short distance, therefore causing a lot of local damage (such as cell destruction). Radioisotopes for therapeutic use stay longer in the body than imaging ones; this is intentional in order to increase treatment efficiency, but this remains limited to several days."

Compared to commonly used medicinal products they have a short history of use. Their development is strongly related with the development of the manufacturing techniques of the radioisotopes which they contain and the development of high tech diagnostic equipment and advanced (targeted) cancer treatment. Market for Radiopharmaceuticals is growing as there is an increasing need for these kind of products as the prevalence of cancer is growing.

Characteristics, Definition

To understand how to register a radiopharmaceutical, one needs to understand the challenges of its specific characteristics and the scope of the definition.

> ***Radiopharmaceutical:*** *"Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose)" - [EMA Directive 2001/83/EC* [1]*]*

Radiopharmaceuticals have specific characteristics which differ from other medicinal products. They have relatively short expiration date, due to their radioactive decay. The physical half-life (duration that halves radioactivity) of the medical radionuclides varies between few hours to few days.

Because of the short expiration date Radiopharmaceuticals (especially for diagnostic use) are often prepared shortly before use. To overcome the distribution challenges related to this short expiration date, Radiopharmaceuticals are often prepared close to the user/ patient. This leads to the use of semi-manufactured products like radionuclide generators, kits and radionuclide precursors.

> ***Radionuclide generator:*** *"Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical. '*
> ***Kit:*** *"Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration. '*
> ***Radionuclide precursor:*** *"Any other radionuclide produced for the radio-labelling of another substance prior to administration. "- [EMA Directive 2001/83/EC* [1]*]*

Because of the safety aspects of radiation emitting products, full automatic systems may often be used for synthesis, purification and finished product manufacturing. The manufacturing and distribution chain can be divided over several partners (companies, radiopharmacies, hospitals). The drug substance is often not isolated and released before use as such. Strict control over quality of the starting materials and the full manufacturing process (through validation and IPC monitoring) is essential.

Radiopharmaceuticals are a special class of pharmaceuticals and utmost care should be taken for their handling, storage, dispensing and use. The characteristics which sets them apart from pharmaceuticals include not only their short half-life, but also the inherent hazardous nature of the radioisotope, the issue of maintaining sterility with radiation safety simultaneously, storage, transport and waste disposal issues and the fact that minute change in dose may cause faulty diagnosis or even over exposure. Guidelines applicable to pharmaceuticals are therefore not always relevant to radiopharmaceuticals and therefore specific guidelines have been developed.

MAA for Human Medicinal Products, DIR 2001/83/EC

Is a radiopharmaceutical a human medicinal product and under what conditions does it require registration?

Radiopharmaceuticals (including semi-manufactured products) fall within the scope of human medicinal products definition according to art. 2a: having properties for treating or preventing disease in human beings (Radiotherapeutics) and art. 2b: used in or administered to human beings to making a medical diagnosis (Radiodiagnostics) of Dir 2001/83/EC [1]. If they are industrially produced and placed in the market (sold), they require marketing authorization (MA).

Radiopharmaceuticals that are produced in small scale facilities (e.g. radiopharmacy) are exempted to have a marketing authorization based on “magistral” or “officinal” preparation (art 3.1 and 3.2 of Dir 2001/83/EC [1]). These institutions are usually controlled by national pharmaceutical inspection schemes.

GMP (Industry) versus cGRPP (Radiopharmacy)

Which prerequisites are needed for registration, e.g. which general GMP rules need to be followed for radiopharmaceutical manufacturing?

For industrial scale GMP, annex III “Manufacture of Radiopharmaceuticals” of Eudralex vol. 4 [2] is the quality guidance to follow. For small scale preparations, “Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals” (EANM) [3] and “Guide to Good Practices for the preparation of Medicinal Products in Healthcare Establishments, Annex 3” (PIC/S) [4] have been developed. Additionally, Ph. Eur. 5.19 Extemporaneous preparation of radiopharmaceuticals [5] has been published by EDQM to guide the Radiopharmacist.

Health Agencies, EU Regulatory route

When applying for a registration is there a specific regulatory route for Radiopharmaceuticals? The answer is no, Radiopharmaceuticals follow the same Regulatory submission process and procedures (National, Centralised Procedure (CP), Mutual Recognition Procedure (MRP), Decentralised Procedure (DCP)) as other human medicinal products. A marketing authorization in the EU needs to be applied for at European Medicine Agency (EMA), which is assisted by Committee for Medicinal Products for Human Use (CHMP) for centralized procedure (all EU) and by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) for mutual recognition procedure or decentralized procedure (2 or more EU member states).

Guidelines EU: EMA and EANM

When preparing for registration, how do you know where to comply with? On the European level, specific guidelines have been developed by the EMA [6]–[9].

Furthermore the scientific society, the European Association of Nuclear Medicine (EANM) advocates to EMA for a more universal approach to the requirements for amongst others clinical trial conduct and MA submission. This resulted in some valuable EANM guidelines that guide companies that are operating in the field of radiopharmaceuticals [3], [10]–[17].

Drug substance, Drug product, Manufacturing processes

Challenges when preparing for a radiopharmaceutical registration are amongst others: the definition of the "Drug substance", the manufacturing process aspects for drug substance and finished product (including safety aspects and control), dosing, stability studies etc. To understand those challenges some particular aspects are described in more detail below.

Radionuclide

A radiopharmaceutical preparation contains its radionuclide:

- as an element in atomic or molecular form
- as an ion
- included in, adsorbed on or attached to molecules by chelation

Usually, radiopharmaceuticals contain two major components:

- A radionuclide that provides the desired radiation characteristics
- A chemical compound with structural or chemical properties that determine the in vivo distribution and physiological behavior of the radiopharmaceutical

Radionuclide production

Radionuclides can be produced in the following ways:

1. In reactions of neutrons (nuclear fission, target irradiation (neutron activation) in nuclear reactors; carriers may be added to increase yield)
2. In reactions of charged particles, typically protons, deuterons or alpha particles. Target undergoes nuclear fragmentation upon being hit by high energy particle beam to give rise to new radionuclides (target irradiation using accelerators, in particular cyclotrons; product is not isotopic with target, carrier-free)
3. By its separation from radionuclide generators (chemical or physical separation of a daughter (short half-life) radionuclide from a parent radionuclide (long half-life). Parent radionuclides can be produced in either nuclear reactors or cyclotrons)

The use of a carrier in the process is influencing the purity of the radionuclide. It needs to be addressed in the registration file.

Isotopic carrier: A stable isotope of the element concerned either present in or added to the radioactive preparation in the same chemical form as that in which the radionuclide is present

Carrier-free preparation: A preparation free from stable isotopes of the same element as the radionuclide concerned present in the preparation in the stated chemical form or at the position of the radionuclide in the molecule concerned

No-carrier-added preparation: A preparation to which no stable isotopes of the same element as the radionuclide concerned are intentionally added in the stated chemical form or at the position of the radionuclide concerned

Radionuclide processing

The radionuclides obtained from a generator, cyclotron or reactor (typically termed 'primary labelling precursor') are obtained in simple ionic or molecular forms. As such, they are often not necessarily useful as imaging agents themselves. Synthetic chemistry techniques are used to incorporate these primary precursors into a molecule of interest directly or via the generation of intermediate labelled building blocks (often termed secondary radiolabeling precursors. Each of the steps in the synthetic process (from primary precursor through to final product) should be carefully optimized to reduce production times and maximize yields and quality of the radiopharmaceutical products. Such optimization may include choice of the reaction solvent, reaction temperatures, improvements in technical handing, purification, etc. Radionuclide processing may be executed at another company as where production takes place.

Synthesis modules: automation/ purification/ formulation and sterilization

In order to reduce radiation exposure to staff in the processing of radionuclides from primary precursor through to final purified product, these activities are often performed behind lead shields (lead bricks, hot-cells) often using automated devices ('synthesis modules'). The final product may need purification (e.g. HPLC, solid phase extraction) prior to formulation and sterilization. The latter is most frequently performed by passage of the formulated product over a 0.22 micrometer micro membrane filter into a sterile vial and/or autoclaving (reference). Kits containing reagents and consumables are available for a number of radionuclides.

Dosage form, dosage

In most cases radiopharmaceuticals are administered intravenously (and thus require sterility), however, other application modes exist as well. Typical examples for oral administration of radiopharmaceuticals are Iodine-131 capsules or solutions. Another type of administration is applied for example for lung ventilation studies using

Technetium-99m, here the radiopharmaceutical (99mTc-labelled carbon micro particles) is nebulized and inhaled by the patient. Inhalation is as well used if the radiopharmaceutical by its nature is a gas, such as [15O]oxygen or Xenon-133.

For diagnostic radiopharmaceuticals the amount of radioactivity that is given to the patient depends mainly on the sensitivity of the camera system, since the radiation exposure caused by a diagnostic radiopharmaceutical should be kept as low as possible. In contrast, the amount of radioactivity given for therapeutic purposes is determined by the energy dose that should reach the target organ. Commercially available therapeutic radiopharmaceuticals are often prescribed according to body weight.

Dossier: Quality (CMC)

In order to register a medical dossier is to be compiled. What should be in the dossier for a Radiopharmaceutical? For European Human Medicinal Product submission dossiers general guidance on presentation and format of the dossier are presented in Volume 2B of Notice to Applicants (NTA), Medicinal products for human use. [18]. For detailed aspects specific for Radiopharmaceuticals, reference is made herein to Annex to Module 3 (Part A), which again refers to the "Note for guidance on radiopharmaceuticals 3AQ20" (1990). This note for guidance has been followed up by EMA Guideline on Radiopharmaceuticals [6]. Some aspects from this guideline are highlighted below.

32S considerations: General aspects

- Radioactive drug substances are as a rule not isolated; they are usually presented as solutions.
- Radioactivity should only be expressed in Becquerel at a given date, and time if appropriate. If a calibration time is stated, the time zone used should be stated (e.g. GMT/CET). Where practicable, specific radioactivity, carrier free, non-carrier added or carrier added should be stated.
- The active substance of a radiopharmaceutical kit and the chemical precursor for synthesis of PET radiopharmaceuticals should follow standard guidance on requirements for Active Substances. Information may be presented in a separate 3.2.S section.
- Where an active substance is not isolated during the production process, information on specification may presented in section 3.2.P.5.1. Drug Product Specification(s).

Becquerel: Radioactivity is expressed in Becquerel (Bq) as the SI-unit. One Becquerel is defined as one disintegration per second (dps). Normally, activities used in radiopharmacy are in the range of megabecquerel (MBq) or gigabecquerel (GBq). There is a non-SI-unit for radioactivity called Curie (Ci), which is used in some occasions. One Ci represents the disintegration of one g of radium. The equivalence between the Bq and the Ci is as follows: 1 Bq= 2.7 x 10-11 Ci

1 Ci = 37 GBq

Specific radioactivity: The Radioactivity of a radionuclide per unit mass of the element or the chemical form concerned, e.g. becquerel per gram or becquerel per mole.

32S considerations: Active substance in Specific products

- Radiopharmaceutical: For radiopharmaceuticals prepared from kits, documentation on the chemistry of the active substance can in some cases be obtained and presented differently from what is described in the relevant note for guidance (e.g. some technetium complexes).
- Radionuclide generator: In a radionuclide generator, both mother and daughter radionuclides are to be considered as active substances
- Kit: For radiopharmaceutical kits, the 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. In addition, the radiolabelled form obtained after radiolabelling with a suitable radionuclide should be described.

32P considerations

- For radiopharmaceutical kits a detailed description of the radiolabelling procedure should be given.
- For radionuclide generators a detailed description of the elution procedure should be included. Maintaining sterility is important.
- For radiopharmaceuticals containing radionuclides of short physical half-life (e.g. PET radiopharmaceuticals), that are released parametrically, special attention should be devoted to the purity and control methods for all starting materials, reactants, chemicals, reagents and solvents used in synthesis and purification
- For radiopharmaceuticals, which are synthesized in automated units, including PET radiopharmaceuticals, the unit and all production steps in this unit should be described in detail, including cleaning and steps to avoid contamination where relevant. Indicators of malfunctioning computer control should be stated
- When radiopharmaceuticals are manufactured in situ for direct administration to the patient (e.g. PET radiopharmaceuticals with physical half-life of the radionuclide ≤ 20 min), the consistency of the production process has a particularly great importance.
- For radionuclide generators, details on testing for mother and daughter radionuclides are required.
- For kits, the specifications of the finished product shall include tests on the quality of products after radiolabeling.
- For some radiopharmaceuticals it may not be possible to obtain the results of certain tests, e.g. sterility test, before the product is released. However, these tests are important in the validation of the manufacturing process
- The general stability guidelines are not fully applicable for ready-for-use radiopharmaceuticals, radionuclide generators and radioactive precursors. Specific items are described (e.g. radioactivity at the time of manufacture and batch size requirements)

Quality standards: the Ph. Eur.

One of the registration challenges is how to set up your drug substance and drug product specifications. In order to get a marketing authorization in the EU, pharmaceutical companies need to comply with the official quality control standards (e.g. monographs) as published by European Directorate for the Quality of Medicines and Healthcare (EDQM) in the European Pharmacopoeia (Ph. Eur.). Expert group No. 14 (Radiopharmaceutical Preparations) and the PRP Working Party (Precursors for Radiopharmaceutical Preparations) have contributed to the drafting and revision of monographs in the field of radiopharmaceuticals.

General Monographs are available for Radiopharmaceutical Preparations with a separate table of physical characteristics of radionuclides, Chemical Precursors for Radiopharmaceutical Preparations and (for information only) the Extemporaneous preparation of radiopharmaceuticals.

Individual Ph. Eur. Monographs can be distinguished for:

1 Radiopharmaceutical preparations for direct clinical use
2 Radionuclide precursors, which by definition are radioactive
3 Chemical precursors which are not radioactive

In addition to the monographs, a description of specific test methods are published by EDQM:

- EDQM Guide for the elaboration of monographs on radio-pharmaceutical preparations, edition 2018
- Ph. Eur. general monograph 0125: Radiopharmaceutical preparations, 07/2016
- Ph. Eur. general monograph 2902: Chemical precursors for radiopharmaceutical preparations, 07/2016
- Ph. Eur. general chapter 5.7: Table of physical characteristics of radionuclides, 01/2008
- Ph. Eur. general chapter 5.19: Extemporaneous preparations of radiopharmaceuticals, 04/2016
- Ph. Eur. general method 2.2.66: Detection and measurement of radioactivity, 01/2014

The information in the Radiopharmaceuticals monographs as published by World Health Organization (WHO) in the International Pharmacopoeia presents information that may be supplemental and helpful to the information as presented by the European Pharmacopoeia.

Typical monograph tests

The test parameters for Radiopharmaceuticals that are presented in the monographs which need to be included in the specification in the registration dossier can be very specific to the nature of the product. A Radiopharmaceutical consists of a Radionuclide Part and a Pharmaceutical (or Biological) Part. The quality parameters can be mostly related to either one part. The following specific parameters may apply:

Radionuclide Part

- Identity (Half-life/nature radiation)
- Radionuclidic purity
- Radiochemical purity/ Assay
- Radio Activity/ Half-life
- Physiological distribution

Pharmaceutical Part

- Chemical purity
- pH
- Sterility
- Bacterial endotoxin content (BET)/ Pyrogenicity
- Residual solvents
- General dosage form requirements

(for chemical precursors: tests for assay, metal catalysts, metal reagent residues and microbial contamination may be added to the list of tests)

Because of the short half-life of the radioisotopes, it is not possible to perform all required tests before release of the batch, therefore sterility testing and radionuclide purity are often determined after batch release. The individual tests and test limits for the most commonly used radiopharmaceuticals are described in the European Pharmacopeia.

Typical Ph. Eur. Monographs contents for Radiopharmaceutical:

- 1.2 Monograph title
- 1.3 Definition
    - 1.3.1 Formulae and names
- 1.4 Production
- 1.5 Characters
- 1.6 Identification
- 1.7 Maximum recommended dose in milliliters
- 1.8 Tests
    - 1.8.1 pH
    - 1.8.2 Non-radioactive substances and related substance
    - 1.8.3 Residual solvents
    - 1.8.4 Physiological distribution

  - 1.8.5 Sterility
  - 1.8.6 Bacterial endotoxin
- 1.9 Radionuclidic purity
- 1.10 Radiochemical purity
- 1.11 Radioactivity
- 1.12 Storage
- 1.13 Labelling
- 1.14 Impurities

Closing remarks

Radiopharmaceuticals are a special kind of products with specific characteristics for which specific regulatory guidelines have been developed. The radiopharmaceutical products are quite young and the market is growing, as the need for these kind of products is growing. A successful registration starts with a proper definition and understanding of the product. Within the production of radiopharmaceuticals one can distinguish industrial/GMP and Radiopharmacy/ cGRPP production, which draws the line for the need of a marketing authorization in the EU. Being considered as Human Medicinal Products under Dir 2001/83/EC [1] Radiopharmaceuticals are to be registered through the same regulatory agency (EMA/CMDH/HMP) and regulatory routes. The same basic contents and formats of the regulatory dossier are to be applied to Radiopharmaceuticals. However because of the radioactive nature of the radiopharmaceuticals pharmaceutical guidance can often not be fully applied, therefore EMA and EANM have provided specific guidance for Radiopharmaceuticals. EDQM has published some essential monographs to enable applicants to set their specifications and meet quality standards. Because new diagnostic and therapeutic products are continuously being developed, guidance is still improving and changing. Different regions have developed different regulatory definitions and guidelines (historically). Region specific guidance needs to be consulted to enable a successful and smooth regulatory process, especially in case of national registrations.

If you need help registering your radiopharmaceutical, e.g. preparing and filing your marketing authorization application, don't hesitate to contact the regulatory experts of Starodub B.V.

References

[1] European Parliament and the Council of the European Union, "DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use."

[2] European Commission, "EudraLex Volume 4: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 3 Manufacture of Radiopharmaceuticals."

[3] P. Elsinga *et al.*, "Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals," *Eur J Nucl Med Mol Imaging*, 2010, doi: 10.1007/s00259-010-1407-3.

[4] PIC/S, "Guide to Good Practices for the preparation of Medicinal Products in Healthcare Establishments," *PE 010-4*, 2014.

[5] European Directorate for the Quality of Medicines, "Ph. Eur. 5.19 Extemporaneous preparation of radiopharmaceuticals."

[6] EMA, "Guideline on Radiopharmaceuticals," *EMEA/CHMP/QWP/306970/2007*.

[7] EMA, "Guideline on the non-clinical requirements for radiopharmaceuticals," *EMA/CHMP/SWP/686140/2018*.

[8] EMA, "Guideline on clinical evaluation of diagnostic agents," *CPMP/EWP/1119/98/Rev. 1*, 2009.

[9] EMA, "Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals," *EMA/CHMP/167834/2011*.

[10] S. Todde *et al.*, "Guideline for the preparation of an Investigational Medicinal Product Dossier (IMPD)," *Eur J Nucl Med Mol Imaging*, 2014, doi: 10.1007/s00259-014-2866-8.

[11] A. Verbruggen *et al.*, "Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU," *Eur J Nucl Med Mol Imaging*, 2008, doi: 10.1007/s00259-008-0853-7.

[12] J. Koziorowski *et al.*, "Position paper on requirements for toxicological studies in the specific case of radiopharmaceuticals," *EJNMMI Radiopharm. Chem.*, 2016, doi: 10.1186/s41181-016-0004-6.

[13] J. Aerts *et al.*, "Guidance on current good radiopharmacy practice for the small-scale preparation of radiopharmaceuticals using automated modules: a European perspective," *2014*, doi: 10.1002/jlcr.3227.

[14] EANM Radiopharmacy Committee, "Guidelines on current Good Radiopharmacy Practice (cGRPP) in the preparation of radiopharmaceuticals," 2007.

[15] EANM Technologist Committee, "The Radiopharmacy, A Technologist's Guide," 2008.

[16] EANM and Nuclear Medicine Section of the European Union of Medical Specialists, "European Nuclear Medicine Guide," 2018.

[17] EANM, "Dosage Card," *EANM*, 2016.

[18] European Commission, "Eudralex Volume 2B: Notice to Applicants, Medicinal products for human use, Presentation and format of the dossier, Common Technical Document (CTD)."

About Starodub

Reliable, Efficient and Knowledgeable

Starodub BV was founded in May 2014. The company started with one employee, the founder Valentyna Starodub. By today, our team has grown to round 20 employees and has a valuable network of specialized experts. We partner with (bio)pharmaceutical and medical device companies worldwide to ensure that regulatory requirements are met and business goals, such as quick market access and compliance, are achieved. Please check the Our services page to learn how we can support you with meeting your business goals.

Our lean and powerful team strives to be of added value to our clients. All employees are highly educated and obtained degrees in pharmacy, chemistry, biology or related. Our short reporting lines are key to finding the most efficient road to your success. One of our experts will be your primary contact and the team's collective knowledge and resources are available to give reliable advice and execute projects in the most efficient way. Together, we connect the dots and look beyond the scope of projects to make sure all aspects of importance are addressed.

At Starodub BV consistency and assurance of quality are considered as being highly important. A quality management system has been implemented and we strive to comply with GxP and ISO 9001/13485 constantly. In addition, we have an external board of control, acting as the sparring partner to set the optimal course for our company.

We strive to be a true partner to Our clients, who rate our services as ≥4.5 on a scale of 1 (poor) to 5 (excellent). This motivates us to maintain the highest professional standards and to implement continuous improvement.

About the Author

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Tonja van Dommelen is a former Senior RA Manager of Starodub BV (2014-2019). She is an expert on quality aspects of small molecule products and medical devices. In case you would like to ask a question on this white paper, please contact Valentyna Starodub at info@starodub.nl.