Universidade de Aveiro
Ano 2021

ANA DANIELA VEIGA BATISTA

Relatório de Estágio Curricular em Assuntos Regulamentares realizado no Instituto de Ciências Nucleares Aplicadas à Saúde

Curricular Internship Report in Regulatory Affairs held at the Institute for Nuclear Sciences Applied to Health

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Gestão da Investigação Clínica, realizada sob a orientação científica da Doutora Maria Teresa Ferreira Herdeiro, Professora Auxiliar do Departamento de Ciências Médicas da Universidade de Aveiro.

o júri

presidente	Professora Doutora Margarida Sâncio da Cruz Fardilha Professora Auxiliar C/ Agregação, Universidade de Aveiro
arguente principal	Doutora Maria de Fátima dos Santos Marques Roque Professora Adjunta, (7040) Instituto Politécnico da Guarda - Escola Superior de Saúde da Guarda
orientador	Professora Doutora Maria Teresa Ferreira Herdeiro Professora Auxiliar, Universidade de Aveiro

agradecimentos

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palavras-chave

Assuntos regulamentares, medicamento, medicamento radiofarmacêutico, medicamento experimental, processo de desenvolvimento de um medicamento, investigação clínica, pedido de autorização de ensaio clínico, pedido de autorização de introdução no mercado, radiofarmácia, desenvolvimento radiofarmacêutico, Tomografia por Emissão de Positrões.

resumo

O presente relatório consiste numa compilação das atividades e projetos desenvolvidos durante o estágio curricular em assuntos regulamentares realizado no Instituto de Ciências Nucleares Aplicadas à Saúde. O estágio pretende complementar os conhecimentos teóricos adquiridos anteriormente e desenvolver competências necessárias para uma eficiente e autónoma realização de atividades relacionadas com os assuntos regulamentares.

Na primeira secção do relatório é descrito o estado-de-arte do processo de desenvolvimento de um medicamento e de um medicamento radiofarmacêutico e apresentados a base legal, diretrizes e documentos orientadores relevantes para várias etapas do processo de desenvolvimento.

O estágio permitiu executar atividades associadas à preparação de submissões regulamentares, ao suporte regulamentar a processos de produção e preparação de medicamentos radiofarmacêuticos, e a áreas relacionadas como a pesquisa bibliográfica e a escrita médica.

A realização das atividades propostas juntamente com as várias sessões de formação e discussão, permitiram adquirir e desenvolver competências técnicas e pessoais necessárias à realização de atividades associadas aos assuntos regulamentares. A participação em várias atividades e projetos diferentes, a formação multidisciplinar, o trabalho com uma classe especial de medicamentos (medicamentos radiofarmacêuticos) e o contacto direto com profissionais com expertise e elevado nível de experiência consistiram numa mais-valia para o crescimento profissional e pessoal.

keywords

Regulatory affairs, medicinal product, radiopharmaceutical, investigational medicinal product, drug development process, clinical research, clinical trial application, marketing authorisation application, radiopharmacy, radiopharmaceutical development, Positron Emission Tomography.

abstract

The present report consists of a compilation of the activities and projects developed during the curricular internship in regulatory affairs held at the Institute for Nuclear Sciences Applied to Health. The internship intends to complement the theoretical knowledge acquired previously and to develop the necessary skills for an efficient and autonomous performance of activities related to regulatory affairs.

The first section of the report describes the state-of-the-art of drug and radiopharmaceutical development processes and presents the legal basis, guidelines, and relevant guidance documents for various steps of the development process.

The internship allowed to perform activities associated with the preparation of regulatory submissions, regulatory support for the production and preparation processes, and related areas such as bibliographic research and medical writing.

The execution of the proposed activities combined with the several training and discussion sessions, allowed the acquisition and development of technical and personal skills necessary to perform activities associated with regulatory affairs.

The involvement in several different activities and projects, the multidisciplinary training, the work with a special class of medicinal products (radiopharmaceuticals) and the direct contact with professionals with expertise and high level of experience were an added value for professional and personal growth.

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LIST OF ABBREVIATIONS

ANDA – Abbreviated New Drug Application

AR – Assessment Report

BLA – Biologic License Application

cGRPP – Current Good Radiopharmacy Practice

CHMP – Committee for Medicinal Products for Human Use

CMDh – Coordination Group for Mutual Recognition and Decentralised Procedures - human

CP – Centralised Procedure

CR – Clinical Research

CT – Clinical Trial

CTA – Clinical Trial Application

CTD – Common Technical Document

CTIS – Clinical Trials Information System

CV – Curriculum Vitae

DCP – Decentralized Procedure

EANM – European Association of Nuclear Medicine

EC – European Commission

EFTA – European Free Trade Association

EMA – European Medicines Agency

EU – European Union

FDA – Food and Drug Administration

GCP – Good Clinical Practice

GLP – Good Laboratory Practice

GMP – Good Manufacturing Practice

ICNAS – Institute for Nuclear Sciences Applied to Health

IAEA – International Atomic Energy Agency

ICH – International Conference on Harmonization

IMP – Investigational Medicinal Product

IMPD – Investigational Medicinal Product Dossier

MA – Marketing Authorisation

MAA – Marketing Authorisation Application

MRP – Mutual Recognition Procedure

MSC – Member States Concerned

NCA – National Competent Authority

NDA – New Drug Application

NtA – Notice to Applicants

PET – Positron emission tomography

PI – Principal Investigator

PIP – Paediatric Investigation Plan

PL – Package Leaflet

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RMS – Reporting Member State

SmPC – Summary of Product Characteristics

SSRP – Small-Scale Radiopharmaceuticals

UC – University of Coimbra

USA – United States of America

WHO – World Health Organization

1. INTRODUCTION

The present report, organised in four sections, is the compilation of all the activities developed during the internship in regulatory affairs carried out at the Institute for Nuclear Sciences Applied to Health (ICNAS).

This section consists of the introductory part of the report and presents initially the description of the report structure and posteriorly, a contextualization of the internship, including (a) Characterisation of the host institution, (b) Description of the current state-of-the-art of the drug development process of a medicinal product and of a radiopharmaceutical, including the regulatory context in force for each stage, (c) Presentation of the objectives of the internship.

In the second section, “Internship Experience”, the activities performed during the internship are indicated and described in detail.

The third section, "Discussion", presents a critical discussion of the aptitudes and knowledge acquired in the internship. Finally, in the fourth section, "Conclusion", the final considerations regarding the internship are presented.

1.1 Characterisation of the host institution

The Institute for Nuclear Sciences Applied to Health (ICNAS), founded in 2009, is a multidisciplinary research unit of the University of Coimbra (UC), which uses medical imaging modalities (Positron emission tomography (PET), Magnetic resonance imaging, and computed tomography) for research purposes (basic, non-clinical and clinical research) and to provide specialized health services to the community. In addition to the medical imaging modalities, ICNAS congregates in the same building, a production unit with two particle accelerators (cyclotrons) which are used to produce radioisotopes and a radiochemistry/radiopharmacy unit responsible for the chemical synthesis of radiopharmaceuticals for clinical or research purposes.

The Institute is located in the Health Campus of the UC, close to the Faculties of Medicine and Pharmacy, several research centres and hospitals.

The ICNAS mission (fundamental objectives) consists of: (1) To develop scientific research of multidisciplinary nature, to implement new research techniques within the scope of nuclear technologies applied to health and to disseminate the scientific results of the Institute; (2) To provide specialized health services in the

field of biomedical applications of radiation; (3) To promote inter-institutional collaboration, in the various areas of medical imaging; (4) To promote cooperation with research, education and health care entities.

ICNAS-Production is a company of the UC, located in ICNAS, which is responsible for operating the cyclotrons based in this institute, aiming the production, quality control and availability of radionuclides and radiopharmaceuticals. Additionally, innovation, research, and development of new health technologies (with diagnostic and therapeutic purposes) within the scope of nuclear technologies applied to health is part of the company's mission.

In general, the activities developed at ICNAS can be centred on three main aspects, whereby the functions performed by ICNAS and ICNAS-Production complement each other:

- Production of radionuclides and radiopharmaceuticals for clinical or research purposes (responsibility of ICNAS-Production);
- Research activities (basic, non-clinical and clinical research) (shared responsibilities, ICNAS and ICNAS-Production);
- Provision of specialized health services in the field of biomedical applications of radiation (ICNAS responsibility).

ICNAS has a multidisciplinary team with expertise in medicine, engineering, mathematics, physics, informatics, pharmaceuticals, among others, allowing the adequate execution of all the activities to which it is dedicated (production, research, and service provision) and the fulfilment of the established fundamental objectives.

1.2 State-of-the-art of the drug development process

The pharmaceutical industry is a heavily regulated sector in order to ensure the quality, safety and efficacy of pharmaceutical products (such as, medicinal products), as well as the relevance, robustness and reliability of product information gathered during the development process.[1,2]

As a result of this highly regulatory demanding environment, the area of regulatory affairs has a crucial role in this sector. Regulatory affairs professionals are responsible for knowing and interpreting the current regulatory framework, ensuring compliance with the legal and regulatory requirements at every stage of

the drug development process to ensure that approval is obtained and maintained.[1,3]

Internally, these professionals occupy a central and liaison position between the various functional groups of the organisations (groups responsible for production and quality control, basic, non-clinical and clinical research, surveillance, among others). Externally, they perform an interface and communication role with the regulatory authorities.[1]

During this section, the various stages of the drug development process will be described, identifying the legal basis and the guidelines/guidance documents in force in Europe for various stages of the process. Firstly, demonstrating the regulatory reality associated with medicinal products and then, due to the context of the internship, specifying this issue for radiopharmaceuticals.

1.2.1 Overview of the traditional drug development process

As noted in Directive 2001/83/EC, a medicinal product is defined as "*any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis*".[4]

The drug development process is the process responsible for introducing and maintaining a medicinal product in clinical practice and comprises several phases that aim to develop the medicinal product, obtain data to prove its quality, safety and efficacy for the purpose for which it was developed, and obtain approval from the regulatory authority.[5] It is an expensive, demanding and lengthy process.[6] As observed in Figure 1, traditionally, a medicinal product requires 10 to 15 years to be introduced into clinical practice, and post-marketing authorisation monitoring continues indefinitely, that is, for as long as the medicinal product remains on the market.[6]

The traditional drug development process is described in Figure 1 and comprises the following phases: (1) Drug Discovery; (2) Non-clinical research; (3) Clinical research (CR); (4) Regulatory review and approval process; (5) Large-scale production and distribution; (6) Post-Approval Research and monitoring.[7,8,9]

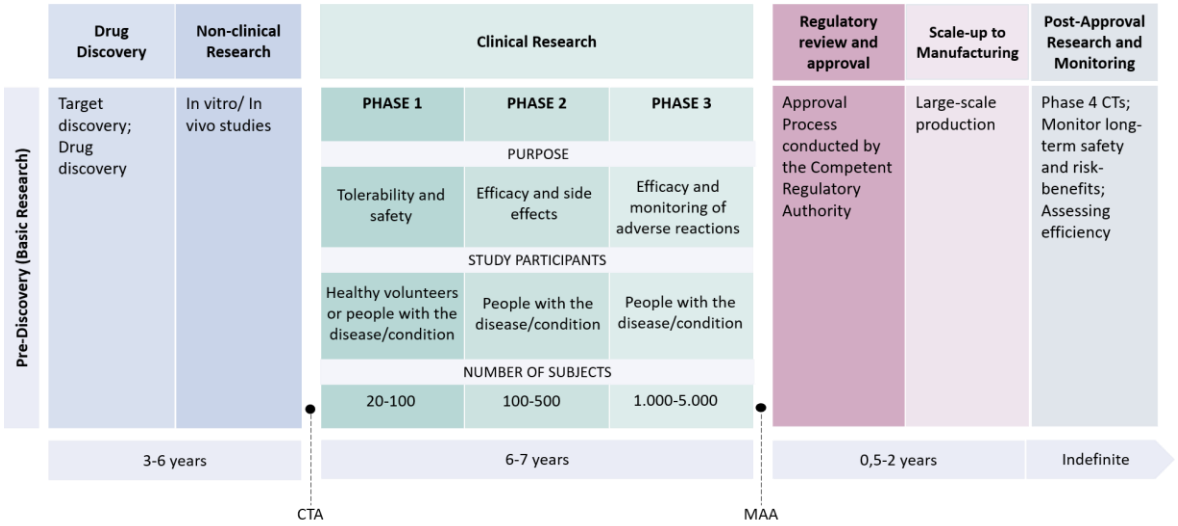

Figure 1. Traditional Drug development. Adapted from "PhRMA 2012 profile" by Pharmaceutical Research and Manufacturers of America, 2012, using information from various references cited in the previous paragraph.
CTA, Clinical Trial Application; MAA, Marketing Authorisation Application; CTs, Clinical Trials

1.2.2 Overview of the radiopharmaceutical development process

A radiopharmaceutical is a radioactive medicinal product, which in its ready-for-use form, consists of two essential components: (1) a radioactive component consisting of one or more radionuclides responsible for emitting an appropriate radiation on its decay and (2) a non-radioactive component that binds to the radionuclide and transports it to the target organ or tissue[10]. Radiopharmaceuticals have an extremely important role in medicine and are used for diagnosis and therapy of several diseases/conditions[11]. The radionuclide used defines the application of the radiopharmaceutical (diagnostic or therapeutic). For diagnostic applications we used radiopharmaceuticals that include radionuclides that decay with the emission of electromagnetic radiation (γ-radiation) that can be detected externally by a gamma camera (SPECT) or positrons (β+) that annihilate with electrons from the surrounding tissue and produce electromagnetic radiation that can be detected by a PET scanner.[12,13] The detected information is then converted into images that reveal the distribution of the radioactive compound in the body, allowing the evaluation of the functional state of an organ and/or the diagnosis of diseases/conditions.[12]

Alternatively, for therapeutic applications, radiopharmaceuticals that decay with the emission of ionising particles (such as α- or β-particles) are generally used. These particles are characterised by their limited range which makes all the energy is emitted in a small area, enabling selective destruction.[12,13]

Four categories of radiopharmaceuticals are considered[14,15]:

- Ready-for-use radiopharmaceuticals, radiopharmaceuticals available in their final form from authorised manufacturers or central radiopharmacies. These medicinal products can be provided in single or multiple doses, may require the preparation of individual doses prior to administration;[12,15,16]
- Non-radioactive components (kits and chemical precursors), preparations and components intended to be reconstituted or combined with the radionuclide(s) in the final radiopharmaceutical prior to administration;[17,15]
- Radionuclide generators, a system used for the production of a final radiopharmaceutical, which contains a parent radionuclide from which a daughter radionuclide is produced by elution or other method;[17,14]
- Radionuclide precursors, a radionuclide used for radioactive radiolabelling of other substances prior administration.[17,14]

Radiopharmaceuticals present some characteristics that distinguish them from the remaining medicinal products, that is, these: (1) Present radioactive properties; (2) Are usually administered in sub-pharmacological doses; (3) Present a short half-life, due to the rapid decay of the radionuclide(s). This characteristic leads, in some situations, to radiopharmaceuticals being released for distribution before the completion of all laboratory quality control tests and the review of laboratory and production data and documentation; (4) Are produced on a relatively small scale compared to the production of conventional medicinal products.[16,18,19]

Because of the characteristics mentioned above, radiopharmaceuticals are recognised as a special group of medicinal products.[17] This class of medicinal products, must comply with the legal and regulatory requirements governing the production and use of medicinal products, however, due to its very own characteristics, the production, preparation and use requires compliance with several specific rules and requirements to ensure the quality of the product and the protection of the operator and the patient.[18,20] The legislative and regulatory framework will be detailed posteriorly.

The process responsible for introducing and maintaining a radiopharmaceutical on the market is described in Figure 2. As with the traditional drug development process, the radiopharmaceutical development process includes six principal phases: (1) Drug discovery; (2) Non-clinical Research; (3) CR; (4) Regulatory

review and approval; (5) Manufacturing and Distribution; (6) Post-Approval research and monitoring.[21,22] Due to the special properties of radiopharmaceuticals, it is recommended that scientific and regulatory advice be used early in the development process, allowing the sponsor to obtain more specific and targeted guidance for the radiopharmaceutical and enabling, through dialogue between the sponsor and the regulatory authority, the enrichment of knowledge and expertise in nuclear medicine.

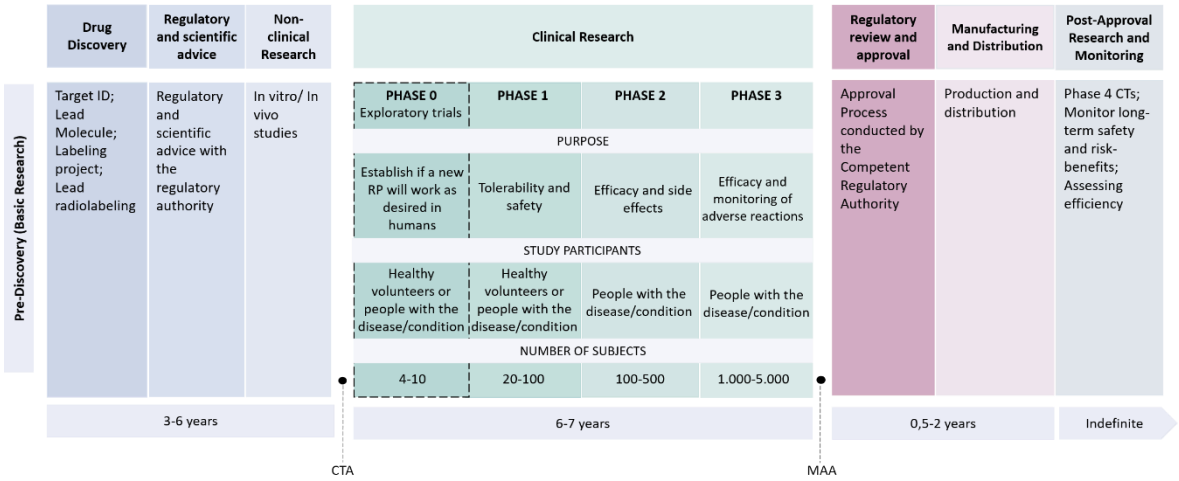

Figure 2. Radiopharmaceutical development process.
CTA, Clinical Trial Application; MAA, Marketing Authorisation Application; CTs, Clinical Trials.

In the radiopharmaceutical development process, the CR phase usually comprises the conduct of exploratory clinical trials (phase 0 clinical trials) using a Microdose approach.[21,22]

An exploratory clinical trial is a clinical trial (CT) which do not present any therapeutic or diagnostic purpose, being developed with the aim of establishing the pharmacokinetic and pharmacodynamic profile of a new investigational medicinal product (IMP) in human beings.[23,24] These studies are conducted prior to conventional phase 1 CTs and use a small number of participants (healthy volunteers or individuals with the disease/condition) who are exposed to sub-pharmacological doses of the IMP during a short period of time.[24] Exploratory CTs use several approaches: Microdose trials (the most widely used approach in the case of radiopharmaceuticals); Single dose trials at sub-therapeutic doses or in the expected therapeutic range; Multiple dose trials.[25]

These studies become relevant since they: (1) Limit the use of animals in the development process; (2) Allow the early evaluation of the product's functionality in the human body, leading that only promising compounds moving to the next phase

of development, saving costs and other resources involved in the process; (3) Constitute a suitable assessment tool when animal models that accurately predict the safety and efficacy of new IMP are absent.[23]

Despite the various advantages inherent in the conduct of exploratory CTs, these are only conducted if they are useful to the product development process and if they ensure the safety of the participants.[24]

Radiopharmaceuticals are often prepared in small quantities for use in CR (exploratory CTs) without undergoing a full development programme to obtain an marketing authorisation (MA).[26] In these situations, the development of the radiopharmaceutical includes the discovery phase and a full non-clinical research phase before use of the radiopharmaceutical in humans, as happens when the aim is to obtain MA.[26]

1.2.3 Description of the drug development phases and identification of the legislative and regulatory framework

In this subsection some of the stages of the drug development (traditional and radiopharmaceutical) identified above will be analysed in detail. Furthermore, the tables, present in the annexes, associated with the legislative and regulatory framework in force in Europe related to each of the phases will be indicated.

The legislative and regulatory framework associated with each of the stages of radiopharmaceutical development was identified using the elaboration of a systematic review. The first step in the review was to define the research question, "What is the legislative and regulatory framework associated with the various stages of the radiopharmaceutical development process?". In a first phase, the databases Pubmed, Scopus and Web of Science were searched in February 2021 using the query: "((radiopharmaceuticals OR "imaging biomarkers" OR tracers OR radiotracers OR pet) AND (regulatory AND (perspective OR aspects OR issues))) AND ("clinical trial application" OR "marketing authorisation" OR "Clinical trials" OR "Non-clinical" OR "drug development" OR "drug life cycle")" to identify studies that reported the legal and regulatory basis associated with the various stages of the development process of a radiopharmaceutical. The chosen search strategy identified a total of 162 results, being that 60 were duplicates. After screening for title and abstract, 22 articles potentially complied with the inclusion criteria and were selected for a reading of the full article. Of these 22 articles, 5 were included

in the systematic review. The legal documents and guidelines identified in these articles were extracted and recorded in the results tables provided in section A of the appendices.

Posteriorly, a search was conducted on the: (1) Websites of various organisations (European Medicines Agency (EMA); International Conference on Harmonization (ICH); World Health Organization (WHO); European Association of Nuclear Medicine (EANM); International Atomic Energy Agency (IAEA)); (2) Websites of the Standing Regulatory Members of ICH (Swissmedic; Health Canada).

On the other hand, the legislative and regulatory framework associated with each of the phases of the medicinal products development were identified through a search on the EMA, ICH and European Commission (EC) websites. Additionally, several documents associated with the legislative and regulatory framework for radiopharmaceuticals identified through the review also presented the legislative and regulatory framework associated with some phases for medicinal products in general.

Regarding radiopharmaceuticals, guidelines and guidance documents developed by non-European regulatory authorities, such as Health Canada, Swissmedic, and Food and Drug Administration (FDA), were also identified. The identification of these documents is intended to provide a greater quantity of resources that present the desired information concerning radiopharmaceuticals. However, the interpretation of information contained in these documents must always be performed considering the European legal framework.

1.2.3.1 Discovery

The discovery phase, the first stage of the drug development process, aims to identify and optimise potential components, capable to treat or diagnose a disease/condition.[27]

Generally, the mechanisms promoting the discovery of new medicines consist of: (1) Identification/recognition of an unmet therapeutic need and subsequent study of the disease/condition to be treated or diagnosed to understand all the mechanisms involved, including those which may have caused the disease and those which may be altered in its presence; (2) Discovery of new characteristics of the diseases/conditions which are central to the process of development of the disease or its symptoms; (3) Identification of a new pharmacological target.[27,28]

This input obtained from the pre-discovery (basic research) phase allows researchers to develop a potential drug capable of counteracting or stopping the effects of the disease/condition or detecting changes caused by the disease, being able to diagnose it.[27,28]

The target identification (gene, protein or other component that has a significant role in the disease/condition or physiological function of an organ), constitutes the first step of the discovery phase. The development of new molecular entities requires targets capable of interacting with a drug and being affected by this (druggable targets).[29] The following stage consists of selected target validation, a process through which the relevance of the target in the disease/condition phenotype is demonstrated.[27] Subsequent processes identify and optimise promising compounds ('lead compounds') that interfere with the selected target to alter the course of the disease or verify alterations caused by the disease.[27,28] If the lead compound is shown to be effective in the various studies it is subjected to, it may eventually become a medicinal product.[28]

When a new drug molecule demonstrates promising therapeutic or diagnostic activity, it is subjected to a characterisation process in terms of size, form, strength, weakness, toxicity, biological activity, among others.[27]

The discovery process of radiopharmaceuticals, like the discovery process of conventional medicinal products, comprises the stages of identification and validation of the target and identification and optimisation of lead compounds.[22,30] Following the identification and characterisation of the non-radioactive component, the radiopharmaceutical design phase proceeds, which includes the selection of the radionuclide and the conjugation method.

There are several factors to be considered during radionuclide selection: (1) Intended application of the radiopharmaceutical (therapeutic or diagnostic); (2) Type and location of the target; (3) Ability to incorporate the radionuclide(s) into the non-radioactive component; (4) Compatibility between the half-life of the radionuclide and the plasma half-life of the non-radioactive component; (5) Mode of decay of the radionuclide; (6) Method of production used.[29,31,32]

The final stages in the design process of a radiopharmaceutical consist of the selection of the radiolabelling method and subsequent labelling of the non-radioactive part.[22] Six major radiolabelling methods are available (isotope

exchange, introduction of a foreign label, labelling with bifunctional chelates, biosynthesis, recoil labelling and excitation labelling).[33]

The Table 6 with the legal basis, guidelines and guidance documents related to the quality of medicinal products and radiopharmaceuticals can be found in Annex A.

1.2.3.2 Non-clinical Research

The non-clinical research phase has the primary objective of determining on the basis of data collected from in vitro studies (laboratory tests) and in vivo studies (animal studies) if the drug identified and optimised in the discovery phase is effective and safe for administration in humans.[27,34] These studies identify the pharmacological properties of the drug (pharmacodynamics and pharmacokinetics) and determine its toxicological profile including, identification of the safe level of the initial dose for first human exposure, determination of parameters for monitoring potential adverse effects and studies of general toxicity and special toxicity (such as, genotoxicity, carcinogenicity, mutagenicity, reproductive toxicity, among others).[35]

According to the European regulatory framework, non-clinical studies must be conducted in compliance with the principles of good laboratory practice (GLP), ensuring the quality, credibility and validity of the data generated.[4,36] However, primary pharmacodynamic studies, which are intended to examine the mode of action and/or the effects of the substance on the target are generally not conducted in accordance with GLP requirements.[25]

For radiopharmaceuticals, the non-clinical studies comprise not only the radiopharmaceutical (the conjugate product) but also the non-radioactive part.[26] In general, pharmacology and general toxicity studies are performed on the non-radioactive component while a biodistribution study including dosimetry is performed on the radiopharmaceutical, allowing to obtain pharmacokinetic data and to investigate radiation induced toxicity.[26,37,38]

Owing to the special characteristics of radiopharmaceuticals, some non-clinical studies are not usually performed in this class of medicinal products: (1) Reproductive and developmental toxicity studies; (2) Genotoxicity/mutagenicity studies, since exposure to these drugs is limited to one or few doses. In some cases, data obtained from structure-activity relationship assessment or Ames test

should be submitted; (3) Carcinogenicity studies. As radiation emitted at the decay of radionuclides is the potential cancer-causing agent, this issue is assessed considering the biodistribution study including dosimetry.[26,39]

As with conventional medicinal products, it is generally expected that non-clinical studies during the course of the radiopharmaceutical development process will be conducted in compliance with the principles of GLP.[26] However, due to the special characteristics of this class of medicinal products, it may not be possible to perform all non-clinical studies in accordance with GLP, thus pharmacological studies, including imaging and biodistribution studies may be performed outside the principles of GLP.[26,40] Toxicity studies should be conducted in compliance with GLP.[26,40]

The legal basis, guidelines and guidance documents associated with the non-clinical development of medicinal products and radiopharmaceuticals are provided in Table 7 in Annex A.

1.2.3.3 Clinical Trial Application

The conduct of a CT in Europe requires the submission of a clinical trial application (CTA) to the competent regulatory authorities.[41,42] A CTA is intended to provide information about the IMP and the CT, including study design, conditions and suitability of research sites, recruitment modality and informed consent process, qualifications of the principal investigator, among others, allowing regulatory authorities to assess the relevance and acceptability of the CT.[43,44]

At the moment of writing this internship report, in the European union (EU), CTAs are submitted under Directive 2001/20/EC, a directive that regulates the conduct of CT with medicinal products for human use, being transposed into the internal right of the member states through national laws (Portugal: “Lei da Investigação Clínica” - Lay no. 21/2014).[45] The construction and implementation of this directive was the first attempt to harmonise the requirements for conducting CT in the EU, however, a public consultation study promoted by the European Commission (EC) revealed that the directive, despite having a positive effect on the safety and credibility of the data obtained in CT, was not successful in promoting CR in Europe, due to several limitations.[46,47] One of the limitations recognised by the study was the absence of harmonised regulatory requirements between Member States.[46]

In order to: (1) Simplify the CTA process, with the development of a single procedure applicable to all Member States, (2) Increase the transparency of CT and (3) Establish a favourable environment for conducting CT in the EU, Regulation No. 536/2014 (Clinical Trials Regulation) was created.[46] Although the Regulation was adopted and went into force in 2014, the moment of its application will happen six months after the confirmation of the full functionality of the Clinical Trials Information System (CTIS) by the EC.[48] The verification of CTIS functionality will be performed through an independent audit and its activation is planned for 31 January 2022.[48] When the Regulation becomes applicable, it will repeal Directive 2001/20/EC and all national legislation in the various Member States created to transpose the Directive.[48] Figure 3 presents a timeframe overview of the transition from Directive 2001/20/EC to Regulation No 536/2014.[45,48]

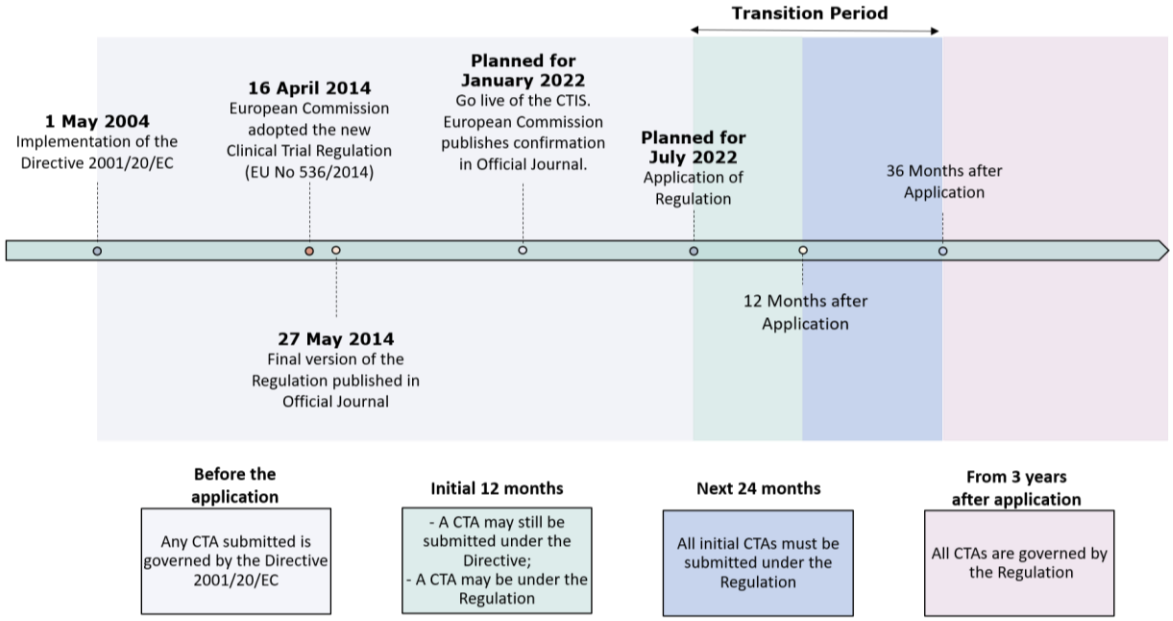

Figure 3. Evolution of the legal basis associated with the CTA procedure throughout time, the transition from Directive 2001/20/EC to Regulation No 536/2014.
CTA, Clinical Trial Application

Table 1 presents a comparative analysis between CTAs submitted under Directive 2001/20/EC and Regulation No. 536/2014, in terms of scope, submission process, application dossier (requirements, structure, and content), and assessment and decision process.[43,44,45,46,49,50]

Table 1. Comparison between CTAs governed by Directive 2001/20/EC and by Regulation No. 536/2014.

Topic	Directive 2001/20/EC	Regulation Eu No. 536/2014
Legal basis	Implemented in national laws	Directly applicable
Scope	Interventional CT with medicinal products for human use	Interventional CT with medicinal products for human use (new category of low-intervention CT)
Submission Process	Multiple submission for one CT (Independent submission for each MS)	Single e-submission to all MSC
Dossier *Requirements*	Not harmonised between MS	One harmonised dossier for all MSC
Structure	Double submission within a MS: One for NCA and one for EC	One dossier: Part I (scientific part) and Part II (national part)
Content	The content of dossier depends on the MS, but in general it includes: NCA: - EudraCT number; - Cover letter; - CTA form; - Protocol and addenda; - Investigator´s brochure (or SmPC); - IMP dossier (with quality data, non-clinical pharmacology and toxicology data and previous clinical trial and human experience data); - Non-investigational medicinal products used in CT; - Other documents (Copy of the opinion of the EC; If the clinical trial is part of an agreed PIP: copy of the Agency's Decision plus opinion of the Paediatric Committee; content of the labelling of the IMP; proof of payment)	Part I (Scientific and Medicinal Product Documentation): - Cover letter; - Application form; - Protocol and addenda; - Investigator´s brochure (or SmPC); - Documentation relating to compliance with GMP for the IMP; - IMP dossier (with quality data, non-clinical pharmacology and toxicology data and previous clinical trial and human experience data); - Auxiliary Medicinal Product Dossier; - If available, a copy of the summary of scientific advice of the Agency (or MS); - If the clinical trial is part of an agreed PIP: copy of the Agency's Decision plus opinion of the Paediatric Committee; - Content of the labelling of

	- Additional national requirements (for example in Portugal: CVs of the coordinating investigator and each of the PI; information regarding the IMP (Manufacturing/import authorisation; GMP Declaration; Certificate of analysis, among others)). EC: - Cover letter; - Application form; - Protocol and addenda; - Investigator´s brochure (or SmPC); - Recruitment arrangements; - Subject information and the informed consent procedure; - Suitability of the PI and quality of the facilities; - Insurance and indemnity; - Financial arrangements; - Proposed other sites and/or countries involved.	the IMPs; - Proof of payment of fee (information per MSC). Part II (National) - Recruitment arrangements (information per MSC); - Subject information, informed consent form and informed consent procedure (information per MSC); - Suitability of the IP (information per MSC); - Suitability of the facilities (information per MSC); - Proof of insurance cover or indemnification (information per MSC); - Financial and other arrangements (information per MSC); - Proof of payment of fee (information per MSC); - Proof that data will be processed in compliance with Union law on data protection.
Assessment *Procedure*	Independent for each MS	Part I: Initial assessment phase (RMS); Coordinated review phase (involving all MSC); Consolidation phase (RMS). Part II: Independent for each MSC.
Duration (from validation to decision)	NCA: 60 days EC: 60 days (+ 30 days for all ATMP and additional 90 days if experts consultation)	Part I: 45days /+ 31days* (26 days – RMS; 12 days – MSC; 7 days - RMS); (+ 50 days for ATMPs) Part II: 45days /+ 31days*. (+ 50 days for ATMPs)

Decision	Decision taken by each MS (NCA and EC)	Part I: Single Decision taken by the RMS; Part II: Decision taken by each MSC.

CT, Clinical Trial; MS, Member State; MSC, Member States Concerned; RMS, Reporting Member State; NCA, National Competent Authority; EC, Ethics Committee; CTA, Clinical Trial Application; IMP, Investigational Medicinal Product; SmPC, Summary of Product Characteristics; PIP, Paediatric Investigation Plan; CV, Curriculum Vitae; PI, Principal Investigator; GMP, Good Manufacturing Practice; ATMP, Advanced Therapy Medicinal Product.

* RMS may extend the assessment period by a maximum of 31 days, for obtaining and reviewing additional information.

The CTAs associated with radiopharmaceuticals, namely in the information submitted to the ethics committee, requires reference to the following basic principles of radiological protection: (1) Justification of activities that may cause or affect radiation exposure; (2) Optimisation of protection to maintain doses as low as possible; (3) Use of dose constraints.[20]

In Directive 2001/20/EC, radiopharmaceuticals (for therapeutic and diagnostic purposes) used in CTs are considered IMPs and therefore comply with the same requirements as any other IMP.[51]

Regulation No 536/2014 introduces some changes in the field of radiopharmaceuticals, presenting distinct requirements depending on the purpose and the context in which they are used. Radiopharmaceuticals with therapeutic purpose are not considered in a special form by the Regulation and thus, they must comply with the same requirements as other IMPs. Contrarily, radiopharmaceuticals with diagnostic purpose present distinct requirements depending on the context in which they are used.[50,51]

The modifications introduced by the Regulation are:[50,51,52]

- No obligation for a manufacturing/import authorisation and consequently no obligation for GMP production of diagnostic radiopharmaceuticals used in CTs conducted in hospitals, health care facilities or clinics by pharmacists or others legally authorised in the Member State.
- Simplified labelling for diagnostic radiopharmaceuticals used as IMPs or Auxiliary Medicinal Products.

The legal basis, guidelines and guidance documents associated with the CTA process for medicinal products and for radiopharmaceuticals can be found in Table 8 in Annex A.

1.2.3.4 Clinical Research

In the context of drug development, the clinical research phase comprises several CTs (studies conducted in humans) with the purpose of answering specific questions about the safety and efficacy of the IMP.[53] As noted in Figure 1 according to the traditional model, the clinical development process of a medicinal product is constituted by four phases that are distinguished by their objectives and study designs. However, as mentioned in the subsection "Overview of the development process of a radiopharmaceutical", some IMPs may benefit from the conduct of exploratory CT (phase 0 CT).

- Phase 1 (Typical study type: Human Pharmacology)

Phase 1 CTs are usually conducted in healthy volunteers, however, depending on the disease and/or IMP properties they may be conducted in patients with the disease/condition to be treated or diagnosed (usually between 20 to 100 participants).[54]

Phase 1 studies have the following objectives: (1) Assess initial safety and tolerability; (2) Determine the pharmacodynamic and pharmacokinetic profile of the IMP; (3) Measure preliminary pharmacological activity. Although phase 1 CTs generally do not present therapeutic objectives, preliminary studies of activity and potential therapeutic benefit may be conducted as a secondary objective.[54,55]

- Phase 2 (Typical study type: Therapeutic Exploratory)

Phase 2 CTs are conducted in patients with the disease/condition to be treated or diagnosed, usually between 100 and 500 subjects, and present as primary objective to analyse the therapeutic efficacy of the IMP.[54]

In detail, Exploratory Therapeutics studies intend to: (1) Assess the effects of the IMP in the intended indication; (2) Analyse the short-term safety of IMP; (3) Determine the appropriate dose/regimen for subsequent studies; (4) Provide data for defining the design, endpoints, therapeutic regimens, methodologies and target populations of future confirmatory studies.[54,55]

- Phase 3 (Typical study type: Therapeutic Confirmatory)

Phase 3 CTs are conducted in a larger number of patients with the disease/condition to be treated or diagnosed, usually between 1.000 and 5.000 participants, and present as their primary objective to confirm that the IMP is safe and effective for use in the intended indication, as demonstrated in phase 2 CTs.[54]

In detail, Confirmatory Therapeutics studies present the following objectives: (1) To demonstrate/confirm the efficacy of the IMP; (2) To determine the safety profile, including pattern and profile of the most frequent adverse reactions; (3) To provide data for evaluation of the risk/benefit balance supporting the MAA; (4) To establish the dose-response relationship; (5) To determine the therapeutic value (global and relative).[54,55]

- Phase 4 (Variety of Studies: Therapeutic Use)

Phase 4 CTs consist of studies conducted after the approval and introduction of the medicinal product on the market. These studies enable to obtain additional information regarding the risks and benefits of the use of the medicinal product in general and/or special populations, to optimise its use and to identify less common adverse reactions.[54,55]

The CTs may be classified according to their phase of development (Phase 1, 2, 3 or 4) or their objectives (human pharmacology studies, exploratory therapy, confirmatory therapy, or therapeutic use). Although a study is characteristic of a certain phase, it may be conducted in other phases of development.[54]

The conduct of a CT requires compliance with a series of legal and regulatory requirements to ensure the protection of the rights, safety, dignity and well-being of the subjects as well as to safeguard the integrity, robustness and reliability of the data generated.[49,50] Currently, the requirements for conducting CTs in Europe are present in two main legal documents, Directive 2001/20/EC which is transposed into the internal right of member states through national legislation (Portugal: Lay no. 21/2014, modified by Lay no. 73/2015) and Directive 2005/28/EC ("Good Clinical Practice" Directive), also transposed into the internal right of member states through national legislation (Portugal: Decree-Law no. 102/2007).[56] When Regulation No. 536/2014 becomes applicable it repeals Directive 2001/20/EC and Directive 2005/28/EC as well as the various national laws created to transpose the Directives.[48,57]

Additionally, several guidelines (Table 9) should be considered when conducting a CT, including the ICH E6 (R2) Guideline (Good Clinical Practice), which reflects the standard international scientific and ethical criteria to be complied during the design, conduct, recording and reporting of CTs.[53]

The performance of a CT comprises several stages: (1) Design of the study; (2) Center identification; (3) Feasibility assessment of the center (Analysis of Feasibility Questionnaire and/or conduct of Qualification Visit); (4) Preparation and submission of the CTA to the national regulatory authorities and ethics committee (addressed in detail in the previous step); (5) Site initiation Visit conducted by the sponsor (or representative) to review the study protocol, processes and procedures, ensuring training and empowerment of the involved team; (6) Study implementation (Recruitment; Follow up; End); (7) Monitoring visits, to verify: that the rights and welfare of participants are protected, enrolment status, the flow of IMPs, that the data collected is accurate, complete and verifiable and that the trial is being conducted in accordance with the protocol and amendments and regulatory requirements; (8) Study Close Out Visit, conducted after ensuring that the study is complete, ensuring: that all case report forms are updated, that all data queries have been resolved, the storage or destruction of laboratory samples, that all study material and IMPs have been accounted, the preparation of records and the notification of the conclusion to regulatory authorities.[53,58,59,60]

During the various stages mentioned above, several stakeholders with well-defined responsibilities are involved.[53,58,61]

In the conduct of a CT associated with the development of a radiopharmaceutical, the exposure of healthy volunteers or patients to ionising radiation should comply with the requirements set out in Directive 2013/59/EURATOM, which presents the basic safety standards for protection against the dangers arising from exposure to ionising radiation, and in the Helsinki declaration and the guidelines for its application.[20]

In addition to the general requirements associated with a CT with a conventional IMP, member states shall ensure for each CR involving exposure to radiation that: (1) The participants are adequately informed of the risks associated with the exposure; (2) Dose constraints are established in situations where the exposed subject has not any direct medical benefit; (3) Dose levels are individually

weighted by a qualified professional and/or prescriber in situations where subjects obtain direct benefit (therapeutic or diagnostic) from the investigational medical practice; and (4) Dose constraints and orientations are established for individuals in contact with exposed subjects.[20,62]

In CRs involving radiation exposure, additional measures should be implemented to reduce the occurrence and magnitude of accidents and the administration of unintended doses.[20,62]

The legal basis, guidelines and documents associated with the clinical development of medicinal products and radiopharmaceuticals are provided in Table 9 in Annex A.

1.2.3.5 Marketing Authorisation Application

If after the drug development process (from the discovery phase to the completion of phase 3 CTs), there is evidence that the IMP is quality, safe and effective for the intended application, the following step for the sponsor consists of submitting a Marketing Authorisation Application (MAA) to the competent authority, national or european, to obtain an MA and to introduce the medicine into the European Economic Area market.[63,64]

The MAA process consists of the submission of a dossier, Common Technical Document (CTD), which compiles administrative information and all required quality, non-clinical and clinical data.[65,66]

CTD is a common format for MAA preparations in all three International Conference on Harmonisation (ICH) regions (Europe, Japan and USA) and in all other countries that recognise ICH standards.[66] A common format for MAAs presents advantages not only for sponsors/applicants such as reducing time and resources in compiling information, eliminating the need to restructure information for different regions, and facilitating the preparation of electronic submissions, but also for regulatory authorities by facilitating the review of applications, improving communication with the sponsor/applicant and simplifying the sharing of information between authorities.[67]

All MAAs in Europe are submitted in the CTD format for all products (new chemical entities, radiopharmaceuticals, vaccines, among others), independently of the procedure used for granting authorisation and of the type of application (full application, generic medicinal products, similar biological medicinal products and

“hybrid” medicinal products applications, among others).[66] However, some application/product types, such as generic medicinal products, may not require some study results, leading to the submission of simplified CTDs where some modules or sections of modules are suppressed.[66]

The CTD is organised into five modules [66,67,68]:

- Module 1: "Administrative Information and Prescribing Information", which comprises the specific administrative documentation required in each region, such as application form, summary of product characteristics, labelling, package leaflet, among others.
- Module 2: "Common Technical Document Summaries", which contains a general introduction of the IMP as well as summaries and overviews of the technical-scientific information detailed in the posterior modules.
- Module 3: "Quality", which provides the chemical, pharmaceutical and biological documentation, describing the technical characteristics of the IMP (Active Substance and Finished Product), such as the manufacturing process, specifications, quality controls, among others.
- Module 4: "Non-clinical Study Reports", which presents a compilation of all documentation relating to the toxicological and pharmacological studies performed.
- Module 5: "Clinical Study Reports", which presents a compilation of all the documentation relating to the clinical trials performed.

In Europe, there are four procedures for granting MAs for a medicinal product, namely, the national procedure, the centralised procedure (CP), the decentralised procedure (DCP), and the mutual recognition procedure (MRP).[64,69] The selection of the MA procedure to be used is based on the consideration of several criteria, such as the classification and nature of the medicinal product, the prior existence of an MA in one of the Member States, the number of Member States in which the medicinal product is intended to be introduced and the company resources available for the submission process.

- *National procedure*

The national procedure is used when the sponsor intends to introduce the medicinal product only on the market of one Member State. In these situations, the application is submitted to the competent authority of the intended Member State

(Portugal: INFARMED I.P.) and the assessment of the application and the granting of the MA is the responsibility of that authority.[64,69]

The preparation and submission of the MAA to the competent authorities in each member state must comply with the national requirements established in national legislation, namely the legislation created to transpose Directive 2001/83/EC (Portugal: Decree-Law 176/2006, "Estatuto do Medicamento"), and in the information provided by the competent authority, as well as with the requirements included in the Notice to Applicants.

- *Centralised procedure*

The MA issued by the CP is valid in all EU member states, including EFTA members Iceland, Liechtenstein, and Norway, allowing rapid and direct access to the European market. The MAA is submitted directly to the European Medicines Agency (EMA), and the evaluation of the application and the formal decision on the authorisation of the medicine is the responsibility of the EMA and the EC respectively.[64,70,71]

In accordance with the Regulation No. 726/2004, the CP is compulsory for: (1) Medicinal products obtained through biotechnological processes; (2) Advanced therapy medicinal products (defined in Regulation No. 1394/2007); (3) Orphan medicinal products (defined in Regulation No. 141/2000); and (4) Medicinal products containing a new active substance for the treatment of: Acquired Immune Deficiency Syndrome, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, or viral diseases.[70,72]

In addition, the CP is optional for MAA for medicinal products with new active ingredients (for other indications than those mentioned above), medicinal products that represent a significant therapeutic, scientific or technical innovation, medicinal products whose authorisation is of public health interest at community level, generic medicinal products whose reference medicinal product has been authorised through this procedure, new MAs that include paediatric indications based on a PIP and MAs for paediatric use.[70,72,73]

- *Decentralised procedure*

Procedure used when the sponsor/company intends to request an MA in more than one EU member state for a medicinal product which does not have a valid MA in any member state and which is outside the scope of the CP.[64]

The MAA is submitted simultaneously to the competent authorities of the member states where the approval is intended, the Reference Member State (RMS) and the Concerned Member States (CMSs). The RMS, selected by the sponsor/applicant, coordinates the assessment process, being responsible for the preparation of the preliminary assessment report that will be subsequently assessed and approved by all the CMSs. At the end of the procedure, if the decision is positive the assessment report (AR), the Summary of Product Characteristics (SmPC), the package leaflet (PL) and labelling as proposed by the RMS are approved and a national MA is obtained in all CMSs.[17,64,70]

- *Mutual Recognition Procedure*

Procedure used when the sponsor/company intends to request an MA in one or several member states for a medicinal product with a valid MA in one EU member state. This Member State, defined as the RMS, performs the first evaluation of the application submitted through a national procedure, granting a national MA. The national MA is the basis for the MA application in other member states where approval is intended, CMSs. CMSs assess and approve all the documentation received (the AR, the SmPC, the PL and labelling), recognising the decision of the RMS.[64,70]

If an CMS refuses to recognise the original MA claiming that the medicinal product may represent a risk to public health, the case should be referred to the Coordination Group for mutual recognition and Decentralised procedures-Human (CMDh) to reach consensus, and if this approach fails, referred to the EMA Committee for Medicinal Products for Human Use (CHMP) for arbitration.[70,74]

Table 2 provides a comparison between the four procedures for obtaining MAs.[64,70,75,76]

The legal basis, guidelines and guidance documents for the MAA procedure for medicinal products and radiopharmaceuticals are presented in Table 10 in Annex A.

Table 2. Comparison between the four procedures (NP, CP, DCP, MRP) for obtaining MAs in the European system.

Topic	NP	*CP*	*DCP*	*MRP*
MA Extension	MA valid only in the MS where the application was submitted and approved	MA valid in all EU MSs including EFTA members Iceland, Liechtenstein and Norway	MA valid in MSs where the application was submitted and approved (RMS + CMS(s))	MA valid in MSs where the application was submitted and approved (RMS + CMS(s))
Entities involved	Evaluation and approval performed by the national competent authority (Portugal: INFARMED I.P.)	Evaluation performed by EMA and approved by CE	Application submitted in several MS simultaneously (RMS prepares a RA that all CMSs evaluate and approve)	Approval by the MSs competent authority, based on the assessment of the MSR (Portugal: INFARMED I.P.)
Timeline	210 days	210 days (EMA) + 67 days (EC)	210 days + 30 days (national phase)	210 days (NP) + 90 days (Updating AR) + 90 days (MRP) + 30 days (National Phase)
Advantages	- Less expensive and faster alternative.	- A single submission process; - A single MA valid for the entire EU; - Medicines are authorised for all EU MSs simultaneously; - Transparent assessment; - Facility in the management of post-approval procedures; - Centralised safety monitoring;	- Eliminates the necessity to undergo several different national procedures; - Not as risky compared to the CP, being able to result in at least one MA; - It includes the CMSs earlier in the assessment compared to MRP, in an effort to minimise disagreements during the assessment and facilitate the obtaining of MAs in as	- Eliminates the necessity to undergo several different national procedures; - Possibility of having a MA valid in several MSs simultaneously.

		- Procedures and responsibilities are well defined; - Product information available in all EU languages at the same time.	many MSs as possible; - The sponsor/applicant selects the RMS; - Possibility of having a MA valid in several MSs simultaneously.	
Disadvantages	- MA valid only for one MS.	- Procedure with restricted access; - "All or nothing"; - Less flexibility in MA updates; - Rapporteur and co-rapporteur are not selected by the sponsor.	- Fees for each MS; - Possibility of having different names associated to the medicine in different MSs.	- Fees for each MS; - Frequently existing disagreements between MSs, delaying the procedure and leading to increased expenditure, due to the use of mechanisms for disagreement resolution; - Possibility of having different names associated to the medicine in different MSs.

NP, National Procedure; CP, Centralised Procedure; DCP, Decentralised Procedure; MRP, Mutual Recognition Procedure; MA, Marketing Authorisation; MS, Member State; EU, European Union; EFTA, European Free Trade Association; RMS, Reference Member State; CMS, Concerned Member States; EMA, European Medicines Agency; EC, European Commission; AR, Assessment Report.

1.3 Internship Objectives

The curricular education undertaken, initially, the bachelor´s degree in Biomedical Sciences and posteriorly the Master´s Degree in Clinical Research Management, allowed the approach and development of knowledge regarding the area of regulatory affairs and the principal activities developed by a regulatory affairs professional. Through this previous knowledge, combined with the perception of the activities performed at ICNAS, it was possible to establish a series of objectives that are expected to be achieved during the internship in regulatory affairs held from October 2020 to June 2021.

During the internship, the increasing involvement in the regulatory affairs activities performed by ICNAS contributed to refining the pre-determined objectives as well as establishing new ones.

Therefore, the principal objectives established were:

- To apply the theoretical knowledge, related to the area of regulatory affairs, acquired during the bachelor's and master's degrees;
- To enhance knowledge and develop skills in a real work environment, making me able to perform the several tasks and activities associated to the regulatory affairs area autonomously and efficiently;
- To obtain specific knowledge regarding radiopharmaceuticals, namely, characteristics that distinguish them from conventional medicines, specific GMP principles and principles of good preparation practice, the various steps of the development process, regulatory and legal requirements required for this class of medicines throughout the development process;
- To be able to identify relevant legal and regulatory documents;
- To be able to critically analyse and interpret legislation and guidelines/guidance documents to establish the necessary requirements (of a medicinal product in general and a radiopharmaceutical) throughout the development process;
- To develop the ability to identify relevant documents that answer questions regarding requirements and other unanswered questions in conventional documents (e.g. through literature review);
- To apply and enrich the ability to perform bibliographical research;

- To acquire the necessary knowledge and competences for the construction of the Investigational Medicinal Product Dossier (IMPD) and the CTD;
- To understand the difference in CTD format associated with the various types of application (full, generic and hybrid), identifying the relevant guidelines for each module in force in Europe;
- To be able to prepare and submit CTA (under Directive 2001/20/EC and Regulation No 536/2014);
- To observe the communication flow and knowledge integration between the group responsible for the regulatory affairs activities and the other activity groups of the host institution;
- To integrate the projects and activities developed by ICNAS, contributing to its realization and success.

Furthermore, some objectives related to soft skills were also established:

- Develop skills in (1) organisation, (2) critical analysis, (3) time management, (4) autonomy, (5) problem solving and (6) teamwork;
- To be able to handle several tasks and projects simultaneously, having the ability to prioritise them taking into account their urgency and importance;
- To improve verbal and written communication skills (portuguese and english).

2. INTERNSHIP EXPERIENCE

The present section has as purpose to indicate and describe in detail the activities and tasks developed during the internship performed at ICNAS.

As mentioned previously, the experience at ICNAS focused on activities and tasks associated with the area of regulatory affairs, however, the internship also enabled the performance of activities in areas adjacent to regulatory affairs and CR, such as medical writing and literature research.

The activities developed during the internship can be grouped in five topics: (1) Regulatory framework of the MA, including MAA and variations to MAs; (2) Format of documentation to be submitted in the context of the MAA; (3) Radiopharmaceuticals, including context of production and preparation, products/materials introduced in the manufacturing process and categories of radiopharmaceuticals; (4) Systematic review in the context of documental support to the MAA for different categories of radiopharmaceuticals; and (5) Project first in human.

Figure 4 intends to present an overview of the activities performed during the internship, identifying the topics addressed, the nature of the activities held in each topic, and the period associated with the execution of the activities related to each topic.

		2020			2021					
Topic	**Nature of the activities Involved**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**
Training										
(1) Regulatory framework of MA (MAA and Applications for variation to a MA)	- Activities of support and preparation of the MAAs; - Activities of support and preparation of the applications for variation to a MA; - Activities of identification, analysis and interpretation of information and documents; - Activities related to the development of technical and practical documentation; - Bibliographic research.									
(2) Format of documentation to be submitted in the context of MAA	- Activities of support and preparation of the MAAs; - Activities of identification, analysis and interpretation of information and documents; - Activities related to the preparation of documents for submission to regulatory authorities; - Bibliographic research.									
(3) Radiopharmaceuticals	- Activities of support to the processes of production and preparation of radiopharmaceuticals; - Activities of support and preparation of the MAAs; - Activities of identification, analysis and interpretation of information and documents; - Activities related to the preparation of documents for submission to regulatory authorities; - Activities related to responding to request for additional information from regulatory authorities; - Bibliographic research; - Medical writing.									
(4) Systematic Review	- Activities of support and preparation of the MAAs; - Activities of identification, analysis and interpretation of information and documents; - Bibliographic research; - Medical writing.									
(5) Project first in human	- Activities to support the radiopharmaceutical "design" process; - Activities to support early development (non-clinical development programme planning); - Activities associated with the CTA; - Activities of identification, analysis and interpretation of information and documents; -Activities related to the preparation of documents for submission to regulatory authorities; - Activities related to the development of technical and practical documentation; - Bibliographic research; - Medical writing.									

Figure 4. Overview of the activities performed during the internship.

2.1 Identification and detailed description of the activities performed during the internship

In the present section, the topics addressed during the internship will be analysed in more detail, identifying, and describing the activities performed in each of them.

2.1.1 Training

During the internship, was enabled to attend some training and discussion sessions that addressed specific issues on the class of radiopharmaceuticals as well as issues related to the area of regulatory affairs. These sessions allowed to

enrich and complement the knowledge acquired previously and autonomously, contributing to a more efficient performance of the proposed activities.

2.1.2 Regulatory framework of the Marketing Authorisation

The internship allowed the execution of several activities associated with the regulatory framework of the MA, namely, preparation and support activities for the MAA process and the submission of variations to the terms of the MAA.

2.1.2.1 Marketing Authorisation Application

The activities related to the subtopic “Marketing Authorisation Application” were performed between 7-16 October and 15-17 December 2020 and intend to: (1) Identify, interpret and consolidate the information regarding the regulatory framework of MAA (Europe) and New Drug Application (NDA) (USA) in a single document to facilitate the selection of the procedure to be used in the European system, present the process in the USA and compare the systems for obtaining approval in the two countries and (2) Propose based on the characteristics of the medicinal product the type of application to submit (complete, generic, hybrid among others).

As mentioned in section 1.2.3.5, the European system has four distinct procedures for obtaining the MA, the national procedure, CP, DCP, and MRP. The selection of the procedure is performed considering the weighting of several criteria, such as classification and nature of the medicinal product, previous existence of an MA in a member state, the extent of MA intended, resources available for the process, and timeline associated with the assessment and approval processes.

In this context, the regulatory affairs professionals analyse the several criteria mentioned above and propose the best registration strategy considering the characteristics of the medicinal product and the resources available in the company for the procedure.

The developed document intends to consolidate the key information in the selection of the MAA procedure and presents several components (characterization of the four procedures, flowchart to support decision-making, comparative analysis of timelines, fees associated with each procedure, and advantages and disadvantages of each procedure) in an attempt to facilitate the decision process.

Similar to the approach in Europe, a medicinal product can only be introduced into the USA market after approval of an New Drug Application (NDA) (or Biologic License Application (BLA) in the case of biological products) by the country's regulatory authority, the FDA.[77,78]

The NDA or BLA process, as well as the MAA process, consists of the submission of a dossier, the CTD, containing all the information related to the technical characteristics of the IMP (such as manufacturing process, specifications, impurities), the toxicological and pharmacological studies and CTs to demonstrate that the medicinal product is of good quality, safe and effective for the indication it was developed for.[78]

It is also available in the USA, the Abbreviated New Drug Application (ANDA) procedure used for generic medicinal products.[77]

Table 3 presents a comparative analysis between the systems for obtaining approval of medicinal products in Europe and the USA.

Table 3. Comparative analysis of the systems for obtaining approval of medicinal products in Europe and the USA.

Topic	Europe	USA
Denomination	MAA	NDA/BLA/ANDA
Entities involved	Several authorities (depending on the procedure used) - EMA (CHMP) and EC; - National competent authorities of each member state;	1 authority - FDA
Registration processes	Several registration processes: NP; CP; DCP and MRP.	1 registration process
Timelines	- 210 days (NP); - 210 + 67 days (CP); - 210 + 30 (National Phase) days (DCP); - 210 (NP) + 90 (Updating AR) + 90 (MRP) + 30 (National Phase) days (MRP).	- 360 days (60 days + 300 days) (Standard review) - 240 days (60 days + 180 days) (Priority review)*

MAA, Marketing Authorisation Application; NDA, New Drug Application; BLA, Biologic License Application; ANDA, Abbreviated New Drug Application; NP, National Procedure; CP, Centralised Procedure; DCP, Decentralised Procedure; MRP, Mutual Recognition Procedure; MS, Member State; AR, Assessment Report; EMA, European Medicines Agency; EC, European Commission; CHMP, Committee for Medicinal Products for Human Use; FDA, Food and Drug Administration.

* Reserved for medicinal products that represent a significant improvement in safety or efficacy over existing treatments. FDA devotes extra resources to these reviews.

The European system presents several types of MAA application.[64] The company, through the regulatory affairs professionals, decides during the early stages of the development process the type of MAA application to use:

- Full application (Article 8(3) of Directive 2001/83/EC). A full application consists of the submission of a complete dossier, as presented in section 1.3.2.3, containing the required administrative information, documentation relating to pharmaceutical testing (physico-chemical, biological or microbiological), non-clinical studies (toxicological and pharmacological) and CTs.[64]
- Generic medicinal products, similar biological medicinal products, and "hybrid" medicinal products applications (Article 10 of Directive 2001/83/EC):
    - Generic medicinal product applications: In this type of application, there is no obligation to submit results of non-clinical studies and CTs if the applicant can demonstrate that the medicinal product is a generic medicinal product, that is, it has the same pharmaceutical form, the same qualitative and quantitative composition in active substance, and whose bioequivalence has been demonstrated through bioavailability studies, in relation to a reference medicinal product which is authorised in the EU for a period not less than eight years.[17,64]
    - Similar biological medicinal product applications: A biosimilar is a medicinal product that is similar to a reference biological medicinal product that is authorised in the EU, despite the variability associated with biological medicines. The similarity is established through comparability studies. In this type of application a CTD is submitted, containing Modules 1 and 2, an expanded Module 3 (full quality documentation with the addition of data obtained from comparability studies), and abbreviated Modules 4 and 5 containing the results of the appropriate non-clinical and clinical studies.[64,79,80]
    - "Hybrid" medicinal product applications: A hybrid medicinal product is a medicinal product similar to an authorised medicinal product. It presents the same active substance, however, (1) it does not comply

strictly with generic medicinal product definition; (2) bioavailability studies cannot be used to prove bioequivalence or (3) there are changes in the active substance, indication, pharmaceutical form, strength, or route of administration. In this type of application, the CTD consists of data from the reference medicinal product and new data.[64]

- Well established medicinal product (bibliographic) (Article 10a of Directive 2001/83/EC): Application used for medicinal products containing an active substance with a well-established use in the community for at least 10 years. These substances have a proven efficacy and an acceptable level of safety. In this type of application, modules 4 and 5 of the CTD consist of appropriate and detailed scientific literature.[64]
- New fixed combination products (Article 10b of Directive 2001/83/EC): Application used when the medicinal product contains active substances used in authorised medicinal products, but which have not been used previously in combination. Modules 4 and 5 of the CTD consist of data related to the combination of active substances.[64]
- Informed consent (Article 10c of Directive 2001/83/EC): Application used when the MA holder of an authorised medicinal product with the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the medicinal product under assessment consents to the use of the quality, non-clinical and clinical documentation.[64]

In the internship, was possible to propose the type of application to use for a medicinal product considering its characteristics, subsequently presenting, the structure of the CTD, and the guidelines to use in the development process and the preparation of the dossier.

2.1.2.2 Variations to Marketing Authorisations

In this topic, it was proposed to identify the requirements for submission of a variation to MA, including the content and structure of the documentation to be submitted as well as the submission process.

A variation is an alteration to the terms of the MA and can be an administrative change (such as a change in the company name and/or address), a quality

change (such as a change in the composition of the product), or a change in the safety, efficacy, and pharmacovigilance of the product.[81]

Variations are classified as minor (types IA and IB) and major (type II) depending on the impact these have on the quality, safety, and efficacy of the medicinal product. Type IA variations have minimal or no impact on the quality, safety, and efficacy of the medicinal product and do not require authorisation before implementation. Type IB variations, as well as type IA variations, do not need formal approval however require notification to regulatory authorities before implementation. Type II variations may have a significant impact on the quality, safety, and efficacy of the medicinal product and require approval before implementation.[81]

Applications for variation to a MA are regulated by Regulation No. 712/2012. Additionally, additional documents are available to facilitate the preparation and submission of variation applications: (1) "*Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures*", (2) pre-submission checklists for variation applications and (3) Notice to Applicants Volume 2B.

The application for variation to a MA should contain the elements set out in Annex IV of the variations regulation and be submitted in the CTD format.

The proposed activities were related to the review of approved drugs, requested in 2019 by the CHMP, to verify the possible presence of nitrosamines, classified as probable carcinogens.

The first task consisted of identifying and describing the steps of the review request as well as identifying the deadlines associated with each step. Subsequently, the outcomes of each step required to be submitted to the regulatory authority were identified and the form in which this information should be submitted was determined, considering that the procedure used is the national procedure.

The following task consisted of determining the information that should be documented and available whenever required by the authority and which demonstrates the outcome of step 1 (risk assessment).

Finally, the requirements and information to be submitted if an application for a variation to the production process and/or product formulation is necessary were identified. Thus, for each possible change required such as a change in the control strategy of the manufacturing process, change of the manufacturing process, or change in the active substance specifications the types of variations to be submitted and subsequently, the format of the documentation to be submitted in each instance were defined.

2.1.3 Format of documentation to be submitted in the context of the Marketing Authorisation Application

The activities related to the second topic were performed between 19 October and 2 November and between 15 and 17 December 2020. The primary objective of the activities performed was to develop a tool to support the elaboration of the CTD for the MAA.

Firstly, a general and detailed comparison between NtA (Notice to Applicants) and CTD was performed to present the principal differences between the two formats and facilitate the reformatting of the NtA format into the CTD format.

The CTD is the mandatory format for MAAs in the EU, since 2003, replacing the NtA format. The two formats have different structures, however, the content that the applicant must provide is similar, despite the addition of supplementary information in the CTD format.[66]

Table 4 presents the general structure of the NtA and CTD formats and a comparison between them.

Table 4. Comparative analysis between the structure of the NtA and CTD formats.

NtA			CTD	
Structure (Parts)		Data	Structure (Modules)	Data
Part I	Part IA	Administrative Data	Module 1	Administrative and prescribing information (application form, product information, EU specific requirements for the
	Part IB	Product Information		

				administrative data Pharmacovigilance information and risk management plan)
	Part IC	Expert Reports	Module 2	CTD sumaries (Quality overall summary, Non-clinical overview/sumaries and Clinical overview/ summaries)
Part II		Chemical, Pharmaceutical, Biological Documentation	Module 3	Quality (Chemical, Pharmaceutical, Biological Documentation)
Part III		Toxico-pharmacological Documentation	Module 4	Nonclinical study reports (Toxico-pharmacological Documentation)
Part IV		Clinical Documentation	Module 5	Clinical Study reports (Clinical Documentation)

NtA, Notice to Applicants; CTD, Common Technical Document.

The development of a tool containing the general and detailed comparison between the two formats intends to facilitate an eventual reformatting of the NtA format into the CTD format.

Subsequently, was permitted to develop a database of guidelines and other guidance documents to support the development process and the preparation of CTD for medicinal products and radiopharmaceuticals and several types of applications.

The database developed is structured according to the CTD format, that is, it is organised into five modules, which are subdivided into several sections. Considering that the database is intended to be applied not only to the development of full applications but also to the application of generic medicinal products, biosimilar medicinal products, and "hybrid" medicinal products, its structure is adapted to the CTD structure required for each type of application. For each section, the guidelines and guidance documents relevant for obtaining the required data and preparing the documentation for the development of the CTD are identified.

The guidelines and guidance documents were identified through a literature search, using various platforms: (1) EMA, ICH, EANM, and IAEA websites; (2) Eudralex, with special attention to Volume 2B of the EU Notice to Applicants and

(3) Literature identified through database searches (Pubmed, Scopus, Web of Science). After their identification, these guidelines were placed in the appropriate section of the database using the following information: Title/Denomination of the document, source, revision, or date for coming into effect of the document, and links to access the document.

In the internship, was also provided the opportunity to contribute to the elaboration of the CTD of a precursor radionuclide, through the developed database.

2.1.4 Radiopharmaceuticals

During the internship were performed some activities specific to the class of radiopharmaceuticals, related to the following topics: (1) Context of production and preparation; (2) Products/materials introduced in the manufacturing process, and (3) Categories of radiopharmaceuticals.

2.1.4.1 Context of production and preparation of radiopharmaceuticals

The activities associated with the subtopic "Context of production and preparation of radiopharmaceuticals" were held between 21 and 23 October 2020 and between 19 February and 2 March 2021. The activities developed aimed to identify, understand, and apply the requirements of GMP and Current good radiopharmacy practice (cGRPP) associated to the production and preparation of radiopharmaceuticals, respectively.

Initially the GMP and cGRPP requirements associated with radiopharmaceuticals were identified and analysed.

Radiopharmaceuticals, as well as the remaining medicinal products, should be manufactured in compliance with the basic principles of GMP established in Directive 2003/94/EC and described in more detail in Volume 4 of Eudralex, Part I (Medicinal Products), Part II (Active Pharmaceutical Ingredients) and relevant annexes, to ensure that they are consistently produced and controlled under the appropriate quality standards, ensuring the continuous production of quality, safe and effective products.[82,83]

Due to the particular characteristics of radiopharmaceuticals (mentioned in section 1.2.2) besides the general requirements, the specific GMP requirements for the

production and control of radiopharmaceuticals provided in annex 3 (Manufacture of Radiopharmaceuticals) should also be considered.[83]

In the context of GMP, principles and guidelines are established relating to all operational and environmental conditions that are associated with production, that is, quality management, personnel, facilities and equipment, documentation, production, quality control, outsourced activities, complaints and product recalls and self-inspection.[83]

The cGRPP, issued by the Radiopharmacy Committee of the EANM, establishes the quality standards associated with the preparation of small-scale radiopharmaceuticals (SSRP) performed in non-industrial sites, such as hospital pharmacies, nuclear medicine departments, PET centres and in general any healthcare establishments. The cGRPP guidelines were divided into two parts due to the different complexities involved in the preparation of radiopharmaceuticals by kits (Part A) and by different chemical procedures (Part B).[84,85]

The cGRPP guidelines intend to provide practice-oriented guidance with sufficient detail for professionals involved in the preparation of radiopharmaceuticals to ensure the appropriate preparation of the radiopharmaceutical and consequently the administration of a quality, safe and effective product.[86]

As well as GMP, cGRPP also establishes principles related to resources, procedures and documentation related to the preparation.[84]

Based on the requirements identified and analysed in the first activity of the present subtopic, a second activity was developed, which consisted in the comparison of the cleanroom requirements associated with the production and handling of radiopharmaceuticals. In this activity, the intention was to develop a document containing a comparison between the cleanroom requirements for the two situations, supported by the principles provided in the guidelines associated with GMP and cGRPP and by several relevant documents identified through a literature search.

As a result of the evolution of regulatory aspects as well as the development of new guidelines, a revised guideline associated with cGRPP was developed and published in February 2021. The guideline presents the structure of the EU GMP guidelines and is divided into three sections: Section 1, which discusses general

aspects that apply to all types of radiopharmaceuticals for diagnostic and therapeutic purposes; Section 2 which addresses the preparation of SSRP using licensed generators, radionuclide precursors or kits; and Section 3 which addresses the preparation of SSRP from non-licensed starting materials or licensed starting materials but with deviations from recommended procedures.[85]

The published guideline was analyzed and interpreted, elaborating subsequently a presentation for training purposes in the institution.

2.1.4.2 Products/materials introduced in the manufacturing process of a radiopharmaceutical

The activity related to the subtopic "Products/materials introduced in the manufacturing process of a radiopharmaceutical" was performed between 1 and 15 April 2021.

The activity consisted of identifying, through a literature search, guidelines, guidance documents, and/or literature that classify the several products/materials introduced in the radiopharmaceutical manufacturing process: (1) Excipients, ingredients and all chemicals that become part of the radiopharmaceutical or that will be in direct contact with the radiopharmaceutical before application (such as, pushing gas, kit reagent); (2) Reagents and reference materials used in quality control; (3) Products related to hygiene (such as, disinfectants, culture medium); (4) Direct materials, that is, materials intended to be in direct contact with the radiopharmaceutical or its ingredients before application (such as, tubes, syringes, cassettes, primary packaging material) and (5) Indirect materials, that is, all other materials which may influence the quality and safety of the radiopharmaceutical.

In the radiopharmaceutical manufacturing process, a wide variety of materials with different degrees of risk, depending on if they are in direct or indirect contact with the radiopharmaceutical, are introduced. This type of material covers several types of regulation. Depending on their classification, they must comply with the requirements set out in the ICH Q7 guideline, in Directive 2001/83/EC transposed into internal right through Decree-Law No 176/2006, in Council Directive 93/42/EEC on Medical Devices, and in Council Directive 98/79/EC of the European Parliament and of the Council on in vitro Diagnostic Medical Devices.

2.1.4.3 Categories of radiopharmaceuticals

The activities related to the subtopic "Categories of radiopharmaceuticals" were held between 3 and 16 November 2020 and between 1 and 5 April 2021.

The principal objective of the activities undertaken in this subtopic was to identify regulatory requirements and other relevant information to support the preparation of MAAs for the various categories of radiopharmaceuticals.

Therefore, the first activity consisted of the identification and characterization of the various categories of radiopharmaceuticals.

As mentioned in section 1.2.2, there are considered four categories of Radiopharmaceuticals (ready-for-use radiopharmaceuticals, non-radioactive components (kits and chemical precursors), radionuclide generators and radionuclide precursors), presenting distinct characteristics.

Subsequently, several components were identified for each category of radiopharmaceuticals, such as the target solution, the synthesis intermediate, the active substance, and the finished product, as well as the regulatory requirements associated with each.

The identification of the above components for each category of radiopharmaceuticals intends to assist in the process of identifying and planning the information to be placed in the various sections of Module 3 of the CTD.

Finally, the regulatory requirements regarding the content of the CTD to be submitted in MAAs for radiopharmaceuticals were identified and analyzed, to identify the requirements specific to each category of radiopharmaceuticals.

During the period from 1 to 5 April 2021, because of the submission of additional information to INFARMED I.P. under an MAA for a precursor radionuclide, a bibliographic research to determine the information on excipients to be submitted in each category of radiopharmaceuticals was performed, with special attention to the category of precursor radionuclides to justify the data entered.

2.1.5 Systematic review

The tasks associated with the fourth topic were performed between 17 November and 11 December 2020 and between 8 March to the present.

Following the execution of the activities related to the subtopic "Categories of radiopharmaceuticals", it became necessary to conduct a more extensive and robust search regarding the documental support of the MAA associated with the

various categories of radiopharmaceuticals, to identify all legal documents, guidelines, guidance documents and published literature addressing this issue.

Thus, it was decided to perform a systematic review with the purposes of (1) identifying and critically evaluating published legislation and regulations for the submission of MAAs for radiopharmaceuticals and (2) identifying and evaluating published literature by the scientific community that addresses the regulation and/or requirements for submission of MAAs for radiopharmaceuticals.

The first task consisted in defining the search strategy, including query determination, selection of the databases to be used as well as the remaining search platforms (authorities' websites, journals, among others) and establishment of the inclusion and exclusion criteria.

Then, the systematic review was registered in Prospero, international prospective register of systematic reviews in health and social care, submitting several key information about the design and conduct of the systematic review, such as title, information about the authors, research question, types of study to be included, databases, type of data and how it will be extracted, among others. The registration number associated with the systematic review is CRD42021241542.

One of the inclusion criteria for registration in Prospero is the absence of a registered systematic review that intends to answer the same research question of the review that we intend to register, thus, before proceeding with the registration of the systematic review, a search was performed on the platform, using the established query.

Subsequently, the performance of the systematic review was initiated, including, extraction of the articles and documents from the databases and other selected research platforms, analysis of the articles and documents obtained, identification and extraction of the outcomes, and redaction of the article (in progress).

Once the writing of the systematic review has been completed, it is expected to be published in a scientific journal.

2.1.6 Project first in human

The activities related to the fifth topic were performed between 14 and 28 December 2020 and between 12 January and 11 March 2021, and the final objective consisted in the preparation of the CTA of a ready-for-use

radiopharmaceutical, a nanobody conjugated to a radionuclide, for the diagnosis of a neurological disease.

The first activity developed consisted of identifying the criteria to be considered when selecting a radionuclide for conjugation with the non-radioactive component. Then, a summary table was built, containing the various characteristics relevant to radionuclide selection associated with commonly used radionuclides for conjugation (Gallium-68 (^{68}Ga), Fluorine-18 (^{18}F), Copper-64 (^{64}Cu), Yttrium-86 (^{86}Y), Bromine-76 (^{76}Br), Zirconium-89 (^{89}Zr), Iodine-124 (^{124}I)), to facilitate the selection of the most suitable radionuclide for conjugation with the nanobody.

Subsequently, to identify the non-clinical requirements associated with the product and establish an appropriate non-clinical development programme, a search was conducted for: (1) guidelines related to the non-clinical development of a radiopharmaceutical; (2) guidelines related to the non-clinical development of radiopharmaceuticals whose non-radioactive component consists of a biotechnology product; (3) radiopharmaceuticals based on antibodies approved by EMA and/or FDA; (4) documents associated with the approved products identified in point 3, presenting non-clinical development; (5) published studies addressing the non-clinical development of similar products.

Through interpretation of the guidelines (Guideline on the non-clinical requirements for Radiopharmaceuticals published by EMA and Clinical Translation of Radiolabelled Monoclonal Antibodies and Peptides published by IAEA), the related document of an approved similar product and the several relevant studies identified, a non-clinical development programme was prepared. The proposed development programme contained the identification of the non-clinical studies to be performed on the non-radioactive part (nanobody) and the radiopharmaceutical (nanobody conjugated to the radionuclide) as well as information regarding the tests that must mandatorily be performed in compliance with the GLP requirements and those that can be performed outside the GLP context.

The following activity consisted of preparing the submission of the CTA to the competent authorities, INFARMED I.P., and the Ethics Committee for Clinical Research (CEIC). Thus, a document was developed containing the: (1) Identification of the content to submit to CEIC and INFARMED I.P., under Directive 2001/20/EC, transposed to internal right through Law No. 21/2014 and under

Regulation No. 536/2014 and (2) Description of the activities to be performed under the CTA submitted under Law No. 21/2014 and Regulation No. 536/2014, with recourse to a flowchart and table of activities. The developed document intends not only to assist in the preparation of the present CTA but also to constitute a useful tool for the preparation of subsequent CTAs submitted under Directive 2001/20/EC and Regulation No. 536/2014.

Subsequently, the IMPD of the product was planned, identifying the structure and content to include in each section.

The IMPD is one of the essential documents that constitute the CTA submitted to the competent regulatory authorities to obtain approval to conduct a CT.[43,50]

The dossier comprises four distinct sections, containing information on (1) quality, manufacturing, and control of the IMP; (2) non-clinical pharmacology and toxicology data related to the IMP; (3) previous CT and human experience data associated with the IMP; (4) overall assessment of the risk/benefit balance of the IMP in the proposed CT. Data associated with sections 1, 2, and 3 should be submitted following a logical structure, similar to the structure of the current version of modules 3, 4, and 5 of the CTD respectively.[43]

2.2 Resume of activities performed

In this section, a resume will be presented regarding the activities performed. This summary intends to associate the various activities and tasks performed in the five topics with the relevant themes associated with the area of regulatory affairs and adjacent areas (MAA, applications for variation to a MA, CTA, regulatory support, bibliographic research, and medical writing) to show in a more succinct form the activities performed related to each theme.

Table 5 consists of a summary table containing the major activities performed in each theme, identifying whether only radiopharmaceuticals or medicinal products in general were addressed.

Table 5. Resume of activities performed during internship.

Theme		Principal activities performed
MAA (of medicinal products and specifically of RPs)		- Accompaniment of an MAA, including preparation, submission, and submission of additional information; - Contribution to the preparation of MAAs, through: (1) Development of support tools; (2) Research and interpretation of relevant documents, regulatory requirements, and published literature.
Applications for variation to MA (of medicinal products and specifically of RPs)		- Identification of requirements, information and format of the documentation to be submitted to the regulatory authority in each type of variation to MA (types IA, IB and II). - Identification of the process of submission to INFARMED I.P. of an application for variation to MA by national procedure.
CTA (of medicinal products and specifically of RPs)		- CTA planning and preparation; - Development of tools to support the preparation of CTAs.
Regulatory support (for RPs)	Production and preparation process	- Identification and interpretation of regulatory requirements; - Consolidation of the requirements associated with the preparation of RPs into a presentation for company training purposes.
	Discovery Process (Design)	- Identification of the criteria to consider in the selection of the radionuclide for conjugation; - Development of a tool to support the process of selection of the most appropriate radionuclide; - Proposal of the most suitable radionuclides for conjugation considering the characteristics of the non-radioactive part and characteristics established for the RP;
	Non-clinical development	- Identification of the legal basis and research of guidelines and other documents containing requirements and other non-clinical information relevant to the characteristics of the product; - Identification of non-clinical requirements; - Development of a non-clinical development programme appropriate to the product.

Bibliographic research	- All the activities developed during the internship involved bibliographic research of guidelines, guidance documents, documents related to approved products, and published literature to identify all the available resources, and thus accomplish all the proposed tasks in the most appropriate, complete, and sustained way; - In particular, in developing the systematic review, a more robust bibliographic research was conducted, following the PRISMA guidelines.
Medical writing	- The principles of good medical writing were applied in the elaboration of the documentation prepared in English and the systematic review.

MAA, Marketing Authorisation Application; MA, Marketing Authorisation; CTA, Clinical Trial Application; RP, radiopharmaceuticals; RPs, radiopharmaceuticals.

3. DISCUSSION

The several tasks performed and accompanied during the internship allowed to complement and enrich the knowledge acquired in the bachelor's and master's degree as well as to develop the necessary skills for an efficient performance of the activities related to the regulatory affairs area.

As presented in the previous section, "Internship Experience", was given the opportunity to perform diversified tasks, associated with several themes such as MAA, applications for variation to MA, CTA, regulatory support to the initial development processes and the production and preparation processes, bibliographical research, and medical writing. The contact with various themes allowed to acquire a higher number of knowledge and skills, consequently allowing the development of the capacity to perform various activities related to regulatory affairs such as: (1) Research, identification, and critical interpretation of legal documents, guidelines, guidance documents, published literature and other relevant documents; (2) Identification, analysis, communication and application of requirements and other relevant information; (3) Planning and preparation of CTA, MAA and applications for variation to MA processes; (4) Preparation of practical and technical documentation.

Throughout the internship, all the proposed activities were developed autonomously, with the proposed resolution being presented afterwards. This autonomy allowed to acquire a greater level of experience and to develop the technical and personal skills necessary to perform activities associated with the areas of regulatory affairs. Additionally, despite being a little intimidating at first, this autonomy contributed to personal and professional growth.

Since the internship was performed in a company whose work product is the radiopharmaceutical, considered as a special class of medicinal products due to its characteristics, it allowed not only to complement the knowledge and develop skills related to the general requirements and processes associated with medicinal products in general but also to acquire specific knowledge to the radiopharmaceutical class and be able to integrate the general and specific requirements. Additionally, the realization of the internship in a multidisciplinary institute proved to be an advantage, insofar as it allowed the contact with several professional areas and backgrounds and to acquire a full perception of the

contribution of all professionals in the process of developing a radiopharmaceutical.

Besides technical and professional skills, the internship enabled to develop soft skills of extreme importance in the areas of regulatory affairs and CR. The main personal skills acquired were autonomy, time management and ability to set priorities, critical thinking, problem-solving, organisation, and teamwork.

The internship also allowed the development of communication skills (written and oral), giving the necessary tools and experience to be able to communicate more clearly and objectively, and to present, justify and argue the point of view more efficiently.

During the internship, was also allowed to apply and enrich the ability to perform bibliographic research, since, in all the topics, to identify all the resources that would address the intended issue a bibliographic research was performed using all the relevant research platforms (websites of organizations and regulatory authorities, databases).

The development of the tools to support the MAA process, namely, the summary document containing the MAA contextualization (topic 1, subtopic “Marketing Authorisation Application”) and the database of guidelines and guidance documents (topic 2), besides enabling to contribute to the preparation of MAAs, allowed to acquire in-depth knowledge on all aspects related to MAAs and develop the ability to prepare MAAs for various types of applications.

Similarly, the tools developed to support the CTA process (topic 5), allowed to acquire in-depth knowledge regarding the process, including, content to be submitted to the competent authorities and flow of activities to be performed for submission of the application, developing the ability to prepare and submit CTAs under Directive 2001/20/EC, transposed into internal right through Law No. 21/2014 and under Regulation No. 536/2014.

The activities performed under the subtopic "Applications for variation to MA", enabled to acquire in-depth knowledge regarding the types of variation (types IA, IB, and II) and the process of submission of a variation to MA to INFARMED I.P., through the national procedure, including the content of the application, the format

of the documentation to submit and submission process, providing the essential tools to be able to submit an application for a variation, in the future.

In the performance of the several tasks associated with the preparation of the systematic review (Topic 4), was allowed to apply, and enrich knowledge, related to the conduct of a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, acquired previously. Additionally, considering that the systematic review involves the extraction of documents and information from various research platforms (databases, journals, and websites of organisations and regulatory authorities), its realisation enables to (1) acquire knowledge and skills related to the use (identification and extraction of results) of databases not previously used; (2) develop the ability to identify relevant documents on websites of various organisations and regulatory authorities; (3) know journals relevant to various areas, especially to the area of regulatory affairs and nuclear medicine; (4) acquire extensive knowledge regarding the documental support of the MAA of radiopharmaceuticals.

The integration in the "First in human" project (topic 5) permitted to acquire knowledge and experience in the performance of several activities supporting the initial phases of the development process and the preparation of the CTA process. This project enabled to develop the following technical (professional) skills: (1) selecting the most suitable radionuclide for conjugation, taking into account the characteristics of the non-radioactive component and the radiopharmaceutical; (2) identifying non-clinical requirements by consulting several relevant documents; (3) preparing a non-clinical development plan taking into account the identified requirements; (4) plan and prepare the IMPD; (5) prepare the CTA process, including identification of the content to be submitted to regulatory authorities as well as the flow of activities to be performed for submission of the application to INFARMED I.P.; (5) consolidate the relevant information in a presentation for efficient communication with the other professionals involved.

Additionally, this project provided the opportunity to develop several personal skills: (1) Teamwork. In this project, there was the opportunity to be integrated into a multidisciplinary team, where the knowledge and work of all the professionals involved complemented each other, to achieve the objective efficiently; (2) Critical analysis. All documents, requirements, and information identified were critically

analysed; (3) Communication skills (written and oral). All relevant information was consolidated in a presentation and later presented and discussed in meetings.

Throughout the whole period of internship, was also enabled to have some training sessions, concerning aspects related to radiopharmaceuticals and to the regulatory affairs area, which allowed, not only to have the necessary support to perform the proposed activities but also to acquire additional knowledge to develop other activities in the future.

All the activities laid out in the activity plan were accomplished. Additionally, due to the needs of the company, some activities that were not previously planned were performed, allowing to further develop the skills, as well as to acquire new knowledge and competences.

At the end of the internship, all the previously defined objectives were achieved (Figure 5).

In general, these 9 months of internship at ICNAS were an enriching experience, providing a lot of learning and enabling the acquisition of useful tools to perform the regulatory affairs activities, not only with the activities undertaken but also with the training and orientation provided by the internship tutor, Dra. Olga Calado. The opportunity to work directly with Dra. Olga Calado, with expertise and a wide professional experience in the field of regulatory affairs, proved to be an asset to the experience.

Established objectives (Section 1.3.)	Topic 1	Topic 2	Topic 3	Topic 4	Topic 5
Apply the theoretical knowledge acquired previously;	✓	✓	✓	✓	✓
Enhance knowledge and develop skills in a real work environment, making me able to perform the several tasks and activities associated to the regulatory affairs area autonomously and efficiently;	✓	✓	✓	✓	✓
Obtain specific knowledge regarding radiopharmaceuticals;	✓	✓	✓	✓	✓
Be able to critically analyse and interpret legislation and guidelines/guidance documents to establish the necessary requirements (of a medicine in general and a radiopharmaceutical);	✓	✓	✓	✓	✓
Develop the ability to identify relevant documents that answer questions regarding requirements and other unanswered questions in conventional documents;			✓		✓
Apply and enrich the ability to perform bibliographical research;	✓	✓	✓	✓	✓
Obtain knowledge regarding the format and content of the CTD and IMPD;	✓	✓			✓
Acquire the necessary skills for building the IMPD and CTD;	✓	✓			✓
Understand the difference in CTD format associated with the various types of application (full, generic and hybrid), identifying the relevant guidelines for each module in force in Europe;	✓	✓			
Be able to prepare and submit CTA (under Directive 21/20/EC and Regulation No 536/2014);					✓
Develop scientific writing skills;			✓	✓	✓
Observe the communication flow and knowledge integration between the group responsible for the regulatory affairs activities and the other activity groups of the host institution;			✓		✓
Integrate the projects and activities developed by ICNAS, contributing to its realization and success;	✓	✓	✓		✓
Organisation;	✓	✓	✓	✓	✓
Time management;	✓	✓	✓	✓	✓
Critical analysis;	✓	✓	✓	✓	✓
Teamwork;			✓	✓	✓
Autonomy;	✓	✓	✓	✓	✓
Ability to set priorities;	✓	✓	✓	✓	✓
Verbal and written communication skills (portuguese and english).	✓	✓	✓	✓	✓

Figure 5. Objectives achieved in the activities and tasks performed in each topic of the internship.

Topic 1: *Regulatory framework of the MA;* ***Topic 2:*** *Format of documentation to be submitted in the context of the MAA;* ***Topic 3:*** *Radiopharmaceuticals;* ***Topic 4:*** *Systematic review in the context of documental support to the MAA for the different categories of radiopharmaceuticals;* ***Topic 5:*** *Project first in human.*

4. CONCLUSION

This report summarises the activities and tasks developed, and the various aptitudes acquired during the curricular internship in regulatory affairs performed at ICNAS under the Master in Clinical Research Management.

In the first section of the report, a systematic review was performed to identify the relevant legal basis, guidelines, and guidance documents for several stages of the medicinal product and radiopharmaceutical development processes. The tables containing the identified information provided in the annexes intend to be a useful consultation tool, integrating in an organised format all regulatory documents relevant to each stage of the development process. This tool becomes particularly useful for radiopharmaceuticals, since the information available for this class of medicinal product is scarcer and more dispersed, being important to consult the documentation developed by organisations such as IAEA, EANM, and by non-European regulatory authorities such as Swissmedic and Health Canada.

At the beginning of the internship the expectation was to acquire the highest level of knowledge and developing the greatest number of skills, technical and personal, essential to the performance of activities associated with the areas of regulatory affairs and CR. Despite the current circumstances and the fact that the majority of the internship was performed in a remote working regime, every activity developed, and all the training and discussion sessions attended, enabled the acquisition of essential aptitudes for the efficient performance of the tasks associated with these areas.

The fact that the internship was performed in an Institute whose work product is the radiopharmaceutical was an added value in the experience, enabling the development of research and critical thinking skills, due to the need to identify all the resources that presented the desired information, and to critically interpret the identified information. Considering that a significant part of the information identified was established in documents developed by non-European authorities and organisations, its interpretation required integration with the European legal framework.

The internship allowed to acquire knowledge and experience in several activities associated with (1) preparation of regulatory submissions, CTA, MAA and

applications for variation to MA, including preparation of documentation (IMPD and CTD) and planning of the submission process, (2) regulatory support, including identification and interpretation of requirements and planning of a programme that complies with the identified requirements, (3) bibliographic research, conducted on every topic covered in the internship to identify the maximum number of documentation addressing the intended issue and a more extensive and robust literature search using PRISMA guidelines conducted on topic 4, (4) medical writing, in the development of the documentation, especially in the writing of the systematic review.

In addition to the several technical skills, the internship also permitted to develop several personal skills essential to the areas of regulatory affairs and clinical research. Among the several skills developed, is highlighted the ability to time management and to establish priorities, critical thinking, communication skills (oral and written), organization, autonomy, and resilience.

At the end of the internship, the important contribution of the share of knowledge and experiences, of the opportunities provided, and of the confidence invested for the professional and personal growth is emphasized.

The internship at ICNAS was a very enriching experience that allowed to complement and enrich the knowledge obtained previously and to develop skills (technical and personal) to be applied in the future in functions associated with regulatory affairs and clinical research.

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ANNEXES

Annex A: Legal basis, guidelines, and relevant guidance documents for each stage of the medicinal product and radiopharmaceutical development process.

Annex B: Activity Plan

Annex A: Legal basis, guidelines, and relevant guidance documents for each stage of the medicinal product and radiopharmaceutical development process.

Quality

Table 6. legal basis, guidelines and guidance documents related to the quality of medicinal products and radiopharmaceuticals.

Medicinal product	Legal Basis	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 (Consolidated version: 16/11/2012). Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.	
	Guidelines / Guidance Documents	Active Substance	Guideline on Active Substance Master File Procedure (CHMP/QWP/227/02 Rev 4/ Corr*) (November 2018). Guideline on the chemistry of active substances (EMA/454576/2016) (November 2016). ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/biological entities) (EMA/CHMP/ICH/425213/2011) (November 2012). Investigation of Chiral Active Substances (April 1994). Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier (CHMP/QWP/297/97 Rev 1 corr) (February 2005). Guidance for the template for the qualified person´s declaration concerning GMP compliance of active substance manufacture “The QP declaration template” (EMA/196292/2014) (May 2014). Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substances (NAS) status of chemical substances (EMA/CHMP/QWP/104223/2015) (December 2015). Recommendation on the Assessment of the quality of medicinal products containing

		existing/known active substances (EMA/CHMP/CVMP/QWP/450653/2006) (February 2009).
	Manufacturing	ICH guideline Q8 (R2) on pharmaceutical development (EMA/CHMP/ICH/167068/2004) (June 2017). ICH guideline Q9 on quality risk management (EMA/CHMP/ICH/24235/2006) (September 2015). ICH guideline Q10 on pharmaceutical quality system (EMA/CHMP/ICH/214732/2007) (September 2015). Guideline on manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015) (July 2017). Guideline on process validation for finished products – information and data to be provided in Regulatory submissions (EMA/CHMP/QWP/BWP/70278/2012-Rev1, Corr.1) (November 2016). Guideline on the sterilisation of the medicinal product, active substance, excipiente and primary container (EMA/CHMP/CVMP/850374/2015) (March 2019). The use of radiation in the manufacture of Medicinal Products (July 1992). ICH guideline Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (November 2000).
	Impurities	ICH guideline Q3A (R2) Impurities in new Drug Substances (CPMP/ICH/2737/99) (October 2006). ICH guideline Q3B (R2) Impurities in New Drug Products (CPMP/ICH/2738/99) (June 2006). ICH guideline Q3C (R8) Impurities: Guideline for residual solvents (EMA/CHMP/ICH/213867/2020) (May 2020). ICH guideline Q3D (R1) on elemental impurities (EMA/CHMP/353369/2013) (March 2019). ICH guideline M7 (R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (EMA/CHMP/ICH/83812/2013) (August 2015).

	Analytical procedures and validation	ICH guideline Q2 (R1) Validation of Analytical Procedures: Text and Methodology (CPMP/ICH/381/95) (June 1995).
		ICH guideline Q4B on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions (June 2017) – and Annexes.
	Specifications	ICH guideline Q6A Specifications: Test Procedures and Acceptance Criteria for New drug Substances and New Drug Products: Chemical Substances (CPMP/ICH/367/96) (May 2000).
		ICH guideline Q6B Specifications: Test procedures and Acceptance Criteria for Biotechnological/Biological Products (March 1999).
		Specifications and control tests on the finished product (June 1992).
	Excipients	Guideline on excipients in the Dossier for application for Marketing Authorisation of a Medicinal Product (EMEA/CHMP/QWP/396951/2006) (June 2007).
		Guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018) (July 2020).
	Packaging	Guideline on Plastic Immediate Packaging materials (CPMP/QWP/4359/03) (May 2005).
	Stability	ICH guideline Q1A (R2) Stability Testing of new Drug Substances and Products (CPMP/ICH/2736/99) (August 2003).
		ICH guideline Q1B Photostability testing of new active substances and medicinal products (CPMP/ICH/279/95) (January 1998).
		ICH guideline Q1C Stability testing: requirements for new dosage forms (CPMP/ICH/280/95) (January 1998).
		ICH guideline Q1D Bracketing and matrixing designs for stability testing of drug substances and drug products (CPMP/ICH/4104/00) (February 2002).
		ICH guideline Q1E Evaluation of stability data (CPMP/ICH/420/02) (August 2003).
		ICH guideline Q1F Stability data package for registration in climatic zones III and IV (CPMP/ICH/421/02) (June 2006).
		Note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99) (March 2001).

			Note for guidance on maximum shelf-life for sterile products for human use after first opening or following reconstitution (CPMP/QWP/159/96 corr) (January 1998).
			Guideline on stability for applications for variations to a marketing authorisation (EMA/CHMP/CVMP/441071/2011-Rev.2) (March 2014).
			Guideline on stability testing: Stability testing of existing active substances and related finished products (CPMP/QWP/122/02, rev 1 corr) (December 2003).
		Pharmaceutical Development	ICH guideline Q8 (R2) on pharmaceutical development (EMA/CHMP/ICH/167068/2004) (June 2017).
			ICH guideline Q9 on quality risk management (EMA/CHMP/ICH/24235/2006) (September 2015).
			ICH guideline Q10 on pharmaceutical quality system (EMA/CHMP/ICH/214732/2007) (September 2015).
			Note for guidance on Development Pharmaceutics (CPMP/QWP/155/96) (January 1998).
			Guideline on the quality requirements for drug-device combinations (EMA/CHMP/QWP/BWP/259165/2019) (May 2019).
			Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) (August 2013).
			Reflection paper on the pharmaceutical development of medicines for use in the older population (EMA/CHMP/QWP/292439/2017) (October 2020).
		Lifecycle management	ICH guideline Q12 on technical and Regulatory considerations for pharmaceutical product lifecycle management (EMA/CHMP/ICH/804273/2017) (March 2020).
Specific to RPs	Legal Basis	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 (Consolidated version: 16/11/2012).	
		Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.	
		Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives	

		89/618/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom.
	Guidelines / Guidance Documents	Guideline on Radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) (November 2008). EU guidelines to good manufacturing practice medicinal products for human and veterinary use, Vol. 4. Annex 3 “Manufacture of Radiopharmaceuticals” (September 2008). Quality Control in the Production of Radiopharmaceuticals; IAEA (2018). EANM guideline on the validation of analytical methods for Radiopharmaceuticals; EANM (2020). Guideline to regulations for Radiopharmaceuticals in early phase clinical trials in the EU; EANM (2008).

RPs, Radiopharmaceuticals; EANM, European Association of Nuclear Medicine; IAEA, International Atomic Energy Agency.

Non-clinical development

Table 7. Legal basis, guidelines and guidance documents associated with the non-clinical development of medicinal products and radiopharmaceuticals.

Medicinal product	Legal Basis		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 (Consolidated version: 16/11/2012). Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (Current consolidated version: 26/06/2019). Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, Regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (Current consolidated version: 20/04/2009).
	Guidelines / Guidance Documents	Non-clinical development	ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995) (December 2009) ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998) (June 2011) ICH S9 Non-clinical evaluation for anticancer pharmaceuticals (EMA/CHMP/ICH/646107/2008) (May 2010)

	Pharmacology and safety pharmacology	ICH S7A Safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00) (June 2001)
		ICH S7B Non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (CPMP/ICH/423/02) (November 2005)
		Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1) (July 2017)
	Pharmacokinetics and toxicokinetics	ICH S3A Toxicokinetics: the assessment of systemic exposure in toxicity studies (CPMP/ICH/384/95) (June 1995)
		ICH S3B Pharmacokinetics: repeated dose tissue distribution studies (CPMP/ICH/385/95) (June 1995)
		Evaluation of control samples for non-clinical safety studies: checking for contamination with the test substance (CPMP/SWP/1094/04) (March 2005)
	Toxicology	Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1 Corr) (March 2010)
		ICH S4 Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing) (CPMP/ICH/300/95) (May 1999)
		ICH S2 (R1) Genotoxicity testing and data interpretation for pharmaceuticals intended for human use (EMA/CHMP/ICH/126642/2008) (June 2012)
		ICH S1A Need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95) (July 1996)
		ICH S1B Carcinogenicity: testing for carcinogenicity of pharmaceuticals (CPMP/ICH/299/95) (March 1998)
		ICH S1C (R2) Dose selection for carcinogenicity studies of pharmaceuticals (EMEA/CHMP/ICH/383/1995) (October 2008)
		ICH S5 (R3) guideline on reproductive toxicology: Detection of toxicity to reproduction for human pharmaceuticals (EMA/CHMP/ICH/544278/1998) (February 2020)

			Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005) (January 2008)
			ICH S8 Immunotoxicity studies for human pharmaceuticals (CHMP/167235/2004) (May 2006)
			ICH S10 Photosafety evaluation of pharmaceuticals (EMA/CHMP/ICH/752211/2012) (August 2015)
			Non-clinical local tolerance testing of medicinal products (EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1) (October 2015)
		Environmental risk assessment	Guideline on the environmental risk assessment of medicinal Products for human use (EMEA/CHMP/SWP/4447/00 corr 2) (June 2006)
Specific to RPs	Legal Basis	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 (Consolidated version: 16/11/2012).	
		Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (Current consolidated version: 26/06/2019).	
		Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, Regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (Current consolidated version: 20/04/2009).	
		Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom.	
	Guidelines / Guidance Documents	Non-clinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018) (November 2018).	
		Position paper on requirements for toxicological studies in the specific case of Radiopharmaceuticals; EJNMMI (March 2016).	

	Guidance documents used in other countries that may be useful for consultation in Europe	Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations Guidance for Industry (FDA-2017-D-5297) (August 2018). Oncology Therapeutic Radiopharmaceuticals: Nonclinical studies and labeling recommendations. Guidance for industry (FDA-2018-D-1772) (August 2019). Guidance for Industry Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals (FDA-2013-S-0610) (November 2011). Developing Medical Imaging Drug and Biological Products. Part 1: Conducting Safety Assessments. Guidance for industry (FDA-1998-D-0035) (June 2004).

RPs, Radiopharmaceuticals; EJNMMI, European Journal of Nuclear Medicine and Molecular Imaging; FDA, Food and Drug Administration.

Clinical Trial Application

Table 8. Legal basis, guidelines and guidance documents associated with the CTA process for medicinal products and for radiopharmaceuticals.

Set of documents applicable to CTA submitted under Directive 2001/20/EC		
Medicinal product	Legal Basis	Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Consolidated version: 07/08/2009). Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

	Guidelines / Guidance Documents	Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (2010/C 82/01) (March 2010). ICH E6 (R2) Good clinical practice (EMA/CHMP/ICH/135/1995) (December 2016). ICH guideline E17 on general principles for planning and design of multi-regional clinical trials (EMA/CHMP/ICH/453276/2016 Rev.1) (December 2017). Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (ENTR/CT 2) (February 2006). Detailed guidance on the European clinical trials database (EUDRACT Database) (ENTR/CT 5) (April 2004). Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004) (March 2006). Guidance on investigational medicinal products (IMPS) and 'Non Investigational Medicinal Products' (NIMPS) (SANCO/C/8/SF/cg/a.5.001(2011)332855) (March 2011). Good manufacturing practices for manufacture of investigational medicinal products (ENTR/F/2/AM/an D(2010) 3374) (February 2010). Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 rev. 1) (September 2018). Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1) (July 2017). Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (2008).

Specific to RPs	Legal Basis	Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Consolidated version: 07/08/2009). Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom.
	Guidelines / Guidance Documents	EANM guideline for the preparation of an Investigational Medicinal Product Dossier (IMPD); EANM (2014). Good Practice for Introducing Radiopharmaceuticals for Clinical Use; IAEA (2015). Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU; EANM (2008). EU guidelines to good manufacturing practice medicinal products for human and veterinary use, Vol. 4. Annex 3 “Manufacture of Radiopharmaceuticals” (September 2008).
	Guidance documents used in other countries that may be useful for consultation in Europe	Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs (FDA-2012-D-0081) (December 2012).

Set of documents applicable to CTA submitted under Regulation EU No 536/2014, once it becomes applicable.		
Medicinal product	Legal Basis	Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Commission Implementing Regulation (EU) 2017/556 of 24 March 2017 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council. Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections. Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use.
	Guidelines / Guidance Documents	Part II Document Harmonisation Guidance (Version 3, November 2020). Detailed Commission guideline of 8 December 2017 on the good manufacturing practice for investigational medicinal products pursuant to the second paragraph of the Article 63(1) of Regulation (EU) No 536/2014 (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials). Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017) (September 2017). Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 rev. 1) (September 2018). Auxiliary Medicinal Products in Clinical Trials (rev. 2, June 2017). Draft - Questions and Answers Document - Regulation (EU) 536/2014 – Version 2.5 (November 2020). Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation (April 2019). ICH E6 (R2) Good clinical practice (EMA/CHMP/ICH/135/1995) (December 2016). ICH guideline E17 on general principles for planning and design of multi-regional clinical trials (EMA/CHMP/ICH/453276/2016 Rev.1) (December 2017). Ethical considerations for clinical trials on medicinal products conducted with minors (September 2017). Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with

		investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1) (July 2017).
Specific to RPs	Legal Basis	Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Commission Implementing Regulation (EU) 2017/556 of 24 March 2017 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council. Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections. Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use. Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom.
	Guidelines / Guidance Documents	EANM guideline for the preparation of an Investigational Medicinal Product Dossier (IMPD); EANM (2014). Good Practice for Introducing Radiopharmaceuticals for Clinical Use; IAEA (2015). Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU; EANM (2008). EU guidelines to good manufacturing practice medicinal products for human and veterinary use, Vol. 4. Annex 3 “Manufacture of Radiopharmaceuticals” (September 2008).
	Guidance documents used in other countries that may be useful for consultation in Europe	Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs (FDA-2012-D-0081) (December 2012).

RPs, Radiopharmaceuticals; EANM, European Association of Nuclear Medicine; IAEA, International Atomic Energy Agency; FDA, Food and Drug Administration.

Clinical Research

Table 9. Legal basis, guidelines and guidance documents associated with the clinical development of medicinal products and radiopharmaceuticals.

Medicinal product	Legal Basis	Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Consolidated version: 07/08/2009) (Until the application of the Regulation (EU) No 536/2014) 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 (Consolidated version: 16/11/2012). Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
	Guidelines / Guidance Documents	ICH E6 (R2) Good clinical practice (EMA/CHMP/ICH/135/1995) (December 2016). ICH Topic E8 General considerations for clinical trials (CPMP/ICH/291/95) (March 1998). ICH Topic E9 Statistical principles for clinical trials (CPMP/ICH/363/96) (September 1998). ICH Topic E10 Choice of Control Group in Clinical Trials (CPMP/ICH/364/96) (January 2001). Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95) (1995). Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) (December 2000).

	Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2) (June 2012). ICH Topic E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data (CPMP/ICH/289/95) (September 1998). ICH Topic E7 Studies in Support of Special Populations: Geriatrics (CPMP/ICH/379/95) (March 1994). ICH guideline E2F on development safety update report (EMA/CHMP/ICH/309348/2008) (September 2011). ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population (EMA/CPMP/ICH/2711/1999) (September 2017). ICH Topic E1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95) (June 1995). ICH E2A Clinical safety data management: definitions and standards for expedited reporting (CPMP/ICH/377/95) (June 1995). ICH Topic E2C (R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (CPMP/ICH/288/95) (June 1997). ICH Topic E4 Dose Response Information to Support Drug Registration (CPMP/ICH/378/95) (November 1994). ICH guideline Q9 on quality risk management (EMA/CHMP/ICH/24235/2006) (September 2015). Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) (2011/C 172/01) (June 2011). ICH Topic E3 Structure and Content of Clinical Study Reports (CPMP/ICH/137/95) (July 1996). Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1) (July 2017). Guidance on investigational medicinal products (IMPS) and 'Non Investigational Medicinal Products' (NIMPS) (SANCO/C/8/SF/cg/a.5.001(2011)332855) (March 2011).

Specific to RPs	Legal Basis	Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Consolidated version: 07/08/2009). Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom.
	Guidelines / Guidance Documents	Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev. 1) (July 2009). Concept paper on the harmonisation and update of the clinical aspects in the authorised conditions of use for radiopharmaceuticals and other diagnostic medicinal products (EMEA/CHMP/EWP/12052/2008) (April 2008). Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU; EANM (2008). Appendix 1 to the guideline on clinical evaluation of diagnostic agents on imaging agents (EMEA/CHMP/EWP/321180/2008) (July 2009)

	Guidance documents used in other countries that may be useful for consultation in Europe	Developing Medical Imaging Drug and Biological Products. Part 3: Design, Analysis, and Interpretation of Clinical Studies. Guidance for industry (FDA-1998-D-0035) (June 2004).

RPs, Radiopharmaceuticals; EANM, European Association of Nuclear Medicine; FDA, Food and Drug Administration.

Marketing Authorisation Application

Table 10. Legal basis, guidelines and guidance documents for the MAA procedure for medicinal products and radiopharmaceuticals.

Medicinal product	Legal Basis	Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. 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 (Consolidated version: 16/11/2012). Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Directive 2004/27/EC (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use). Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

	Guidelines / Guidance Documents	Presentation and format of the dossier-Common Technical Document (CTD); Notice to Applicants - Volume 2B. ICH Topic M4 (R4) Common Technical Document for the Registration of Pharmaceuticals for Human Use – Organisation CTD (CPMP/ICH/2887/99) (June 2016). ICH M4E (R2) Common technical document for the registration of pharmaceuticals for human use – efficacy (EMA/CPMP/ICH/2887/1999) (June 2016). ICH Topic M4Q (R1) Common Technical Document for the Registration of Pharmaceuticals for Human Use – Quality (CPMP/ICH/2887/99) (September 2002). ICH Topic M4S (R2) Common Technical Document for the Registration of Pharmaceuticals for Human Use – Safety (CPMP/ICH/2887/99) (December 2002). ICH Topic E 3 Structure and Content of Clinical Study Reports (CPMP/ICH/137/95) (July 1996). Guideline on summary of requirements for active substances in the quality part of the dossier (CHMP/QWP/297/97 Rev 1 corr) (February 2005). A guideline on Summary of Product Characteristics (SmPC) (R2) (September 2009). Guideline on the packaging information of medicinal products for human use authorised by the union (R14.5) (July 2018). Guideline on the readability of the labelling and package leaflet of medicinal products for human use (ENTR/F/2/SF/jr (2009)D/869) (January 2009). Guideline on excipients in the label and package leaflet of medicinal products for human use (SANTE-2017-11668) (March 2018). Technical guidance on the format of the data fields of result-related information on clinical trials submitted in accordance with articles 57(2) of regulation (EC) NO 726/2004 and article 41(2) of regulation (EC) NO 1901/2006 (SANCO/D/6/SF/mg/ddg1.d.6(2013)84316) (January 2013). Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier (CHMP/QWP/297/97 Rev 1 corr) (February 2005).

Specific to RPs	Legal Basis	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 (Consolidated version: 16/11/2012). Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Directive 2004/27/EC (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use). Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom.
	Guidelines / Guidance Documents	Guideline on Radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) (6 November 2008). Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals (EMA/CHMP/167834/2011) (September 2011).
	Guidance documents used in other countries that may be useful for consultation in Europe	Guidance Document: Radiopharmaceuticals, Kits, and Generators: Submission Information for Schedule C Drugs; Health Canada (July 2019). Guidance Document: Formal requirements HMV4 (Version 7); Swissmedic (January 2021).

RPs, Radiopharmaceuticals

Annex B: Activity Plan

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Universidade Nova de Lisboa
NOVA Medical School | Faculdade de Ciências Médicas, NOVA Information Management School, Escola Nacional de Saúde Pública
Universidade de Aveiro, Departamento de Ciências Médicas
Mestrado em Gestão da Investigação Clínica (MEGIC)

Plano de Atividades

Nome da Instituição: Instituto de Ciências Nucleares Aplicadas à Saúde – Universidade de Coimbra

Nome do Estagiário: Ana Daniela Veiga Batista

Tipo de instituição	
Unidade Orgânica de Investigação da Universidade de Coimbra	

Tópico do Estágio: *Assuntos Regulamentares*

Nome(s) do(s) responsável(is) pelo Estágio (tutor(es))	Formação académica	Cargo na Instituição acolhedora do estágio	Nº de anos de experiência no tópico de estágio	Nº de estágios acompanhados previamente
Olga Calado	Ciências Farmacêuticas	Qualified Person	20	10

Tarefas que constituem o plano de atividades:

Ao longo do estágio a aluna irá interagir com as atividades das áreas indicadas, pretendendo-se que adquira conhecimentos e que consiga executar os procedimentos. Desta forma, no final do estágio deverá ter adquirido autonomia na maioria das tarefas indicadas.

1. Enquadramento Regulamentar no processo de Autorização de Introdução no Mercado (AIM) dos medicamentos (PT/EU/USA)	Assinalar com x
1.1 Tipos de procedimentos de AIM (PT/EU/USA)	X
1.2 Timelines	X
1.3 Esquematizar a informação e com a identificação de vantagens e desvantagens associado a cada tipo de procedimento	X
2. Formato da documentação a submeter no âmbito da AIM	
2.1 Identificar o formato NTA	X
2.2 Identificar o formato CTD	X
2.3 GAP Analysis	X
2.4 Elaboração de base de dados (Guideline/Fonte/Revisão) associado a cada módulo do formato CTD	X
2.5 Identificação do formato anterior (2.4) nos seguintes produtos:	X
2.5.1 Inovadores	X
2.5.2 Genéricos	X
2.5.3 Biossilimares	X
2.5.6 Híbridos	X
2.5.7 Medicamentos radiofarmacêuticos	X
3. Medicamentos Radiofarmacêuticos (radiofármacos(	
3.1 Contexto de fabrico de radiofármacos:	X
3.1.1 Produção em *Good Manufacturing Practice (GMP)*	X
3.1.2 Preparação em meio hospitalar ou clínica, em Current Good Radiopharmacy	X
3.1 Identificar os vários tipos/classificações de radiofarmácos	X
3.2 Identificação dos requisitos regulamentares para submissão de AIM associados a cada tipo de radiofármaco	X
3.3 identificação para cada tipo de radiofármaco:	X
3.3.1 Target solution	X
3.3.2 Composto intermédio de síntese	X
3.3.3 Susbtância ativa	X
3.3.4 produto acabado	X

4. Revisão sistemática	
Elaboração de uma revisão sistemática no âmbito do suporte documental para a submissão de uma AIM de radiofármacos	X
	X
5. Project first in human	
5.1 Enquadramento regulamentar dos produtos envolvidos e respectiva classificação	X
5.2 Identificar os requisitos não clinicos necessários à submissão do pedido de autorização de ensaio clinico	X
	X
	X
	X

Data: 21-01-2021

Assinatura do Aluno

Ana Daniela Veiga Batista

Assinatura do Tutor