Theranostic Radiopharmaceuticals:

A Clinical View on the Approaches to Marketing Approval in the EU and the US

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List of abbreviations, figures and tables

Abbreviations

[^{68}Ga]-PSMA-11	[^{68}Ga]Ga-gozetotide
AAA	Advanced Accelerator Applications
AMRadV	Verordnung über radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel
ANDA	Abbreviated New Drug Application
CDRH	Center for Devices and Radiological Health
CDx	Companion diagnostic
CE	Conformitè Europëene
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional Marketing Authorisation
CMS	Concerned Member State
CT	Computer Tomography
DCP	Decentralised Procedure
Dx	Diagnostic
EANM	European Association of Nuclear Medicine
EEA-EFTA	European Economic Area - European Free Trade Association
EMA	European Medicines Agency
EU	European Union
FAP	Fibroblast activation protein
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
GCP	Good Clinical Practice
GDUFA	Generic Drug User Fee Act
GMP	Good Manufacturing Practice
IND	Investigational New Drug
IVDR	In Vitro Diagnostic Regulation
MA(A)	Marketing Authorisation (Application)
MAH	Marketing Authorisation Holder
MIBG	Metaiodobenzylguanidin
MRI	Magnetic Resonance Imaging
MRP	Mutual Recognition Procedures
NDA	New Drug Application
NETRF	Neuroendocrine Tumor Research Foundation
NIH	National Institutes of Health, a part of the U.S. Department of Health and Human Services, is the nation's medical research agency
NMEU	Nuclear Medicine Europe Association
NRC	Nuclear Regulatory Commission
ODD	Orphan Drug Designation
PDUFA	Prescription Drug User Fee Act
PET	Positron Emission Tomography
PI	Prescribing Information
PMA	Premarket Approval Application
PRIME	PRIority MEdicines

PSMA	prostate specific membrane antigen
RMS	Reference member state
SME	Small and medium enterprises
SmPC	Summary of product characteristics
SNMMI	Society for Nuclear Medicine and Molecular Imaging
SPARC	Stakeholder Political Alliance For Radioligand Cancer Therapies
SPECT	Single Photon Emission Computed Tomography
SSP	Summary of Safety and Performance
SUV	Standard Uptake Value
Tx	Therapeutic
USA/US	United States of America

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1. Introduction

1.1. Aim and Structure of the Thesis

Radiopharmaceuticals are a niche sector in the global pharmaceutical market, but they are growing steadily and the theranostic concept is an important driver in this process [1]. Several people and publications demand streamlined approval processes to overcome the complex regulatory frameworks for theranostic radiopharmaceuticals [1,2]. The aim of this master thesis is to evaluate how theranostic pairs of radiopharmaceuticals can be developed and approved in an efficient and effective way. Consequently, this thesis evaluates the current status of the regulatory framework focusing on clinical aspects of development and approval. Based on development and approval pathways of already marketed radiopharmaceuticals as well as through discussion of regulatory pathways for comparable drugs, the optimal strategy shall be delineated. Furthermore, some suggestion introduced in publications as well as development pathways of radiopharmaceuticals currently under development are considered and critically discussed.

The overall aim is to answer the question whether, given the unique combination of two drugs in a theranostic approach, new regulatory frameworks are needed to foster the (clinical) development of theranostic radiopharmaceuticals.

This first Chapter will introduce the topic of nuclear medicine and theranostics as well as the general drug approval process. It is discussed which radiopharmaceuticals are considered in more detail in this work. In Chapter 2 *Theoretic Theranostic approach*, the theoretic concepts of theranostic development and approval are discussed based on publications and guidelines. The following Chapters 3 *Clinical Trials for Theranostic Radiopharmaceuticals* and 4 *Approval Pathways for Theranostic Radiopharmaceuticals* introduce the clinical trials and approval pathways from already marketed radiopharmaceuticals. Based on these foundations, the theranostic aspects of the approved radiopharmaceuticals is evaluated in Chapter 5. The following part, Chapters 6 and 7, are focusing on potential new frameworks for theranostic development and approvals. These frameworks are derived from comparable drugs and suggestions from published literature. In the concluding discussion all approaches are classified, and a recommendation is given. The main part of the thesis concludes with an outlook.

The thesis has 5 annexes. Annex 1 gives an overview on the legal framework for radiopharmaceuticals. Annex 2 supplement the information on the marketing authorisation ("MA") process given in the introduction. Background information on approval dates, patent situation and market exclusivity are summarized in Annex 3. In Annex 4 the designations for drug approval are introduced and an overview is provided which designations were granted to the discussed radiopharmaceuticals. Annex 5 provides a comprehensive overview on the theranostic radiopharmaceuticals under development including a list of ongoing theranostic clinical trials for a selection of theranostic radiopharmaceuticals.

1.2. Nuclear Medicine and Radiopharmaceuticals

Nuclear medicine is a medical specialty that uses radioactive materials (called radiopharmaceuticals) to diagnose, evaluate, and treat various conditions, particularly those affecting the organs and tissues. The accurate delivery of radionuclides to targeted cells through vectors including small molecules or peptides make it a precision medicine modality.

Radiopharmaceuticals are a special type of drug as they are regulated by both the pharmaceutical legislation (2001/83/EC resp. Code of Federal Regulation ("CFR")) and the radiation protection legislation (Directive 2013/59/Euratom resp. Nuclear Regulatory Commission ("NRC") regulations). A list of applicable regulations and guidelines can be found in Annex 1. Radiopharmaceuticals are defined as any drug which, when ready for use, contains one or more radionuclides (radioactive isotopes). They can be further divided into those intended for diagnostic use, and those with therapeutic indications.

Unlike other imaging techniques like X-rays or magnetic resonance imaging ("MRI"), which primarily focus on the structure of the body, diagnostic nuclear medicine provides information about the function of organs and tissues. Diagnostic radiopharmaceuticals are able to provide unique physiologic temporal and spatial information. The biodistribution of radiopharmaceuticals (tracers) can be visualized by traditional planar imaging or high-resolution cross-sectional trials using either scintigraphy, Single Photon Emission Computed Tomography ("SPECT") or positron emission tomography ("PET") cameras.

Although in total there are worldwide more SPECT tracers approved compared to PET tracer (34 SPECT vs. 20 PET) [3], SPECT tracers have not seen as many recent approvals as PET tracers given the lower resolution and the non-favorable reimbursement [4]. Although historically used as diagnostic part of a theranostic pair, the recently approved SPECT tracers were related to non-theranostic applications like NephroScan (2022, FDA approved Tc-99m succimer) for kidney disease detection. Thus, this thesis focusses on PET radiopharmaceuticals used in a theranostic approach.

Therapeutic radiopharmaceuticals are delivered to the targeted organ, or tissue where they undergo alpha- or beta-decay within the patient, causing radiation damage to the target as well as nearby cells.

1.3. Theranostic Radiopharmaceuticals

Theranostics, a combination of the words "therapeutics" and "diagnostics", is as described in Jadvar et al. [5]

> "*a systematic integration of targeted diagnostics and therapeutics as companion agents*".

This approach

> "*facilitates precision medicine by identifying subsets of patients who would benefit from a particular treatment based on imaging evidence for expression of the intended biological target*" [5].

Theranostics usually refers to two companion drugs with identical or similar structure targeting a specific biological entity for imaging and treatment, thus first imaging a patient's tumor for diagnostics and then therapeutically treat that tumor.

Although the concept has a long history with radioiodine in thyroidology introduced more than 80 years ago, it has experienced remarkable recent renaissance in management of neuroendocrine tumors and prostate cancer. During the last 15 years, publication numbers rose from below 1.000 to nearly 30.000 (see Figure 1). Theranostics is nowadays involving a growing number of scientific disciplines for example the field of nanotechnology [6], nevertheless the approach is still deeply connected with nuclear medicine.

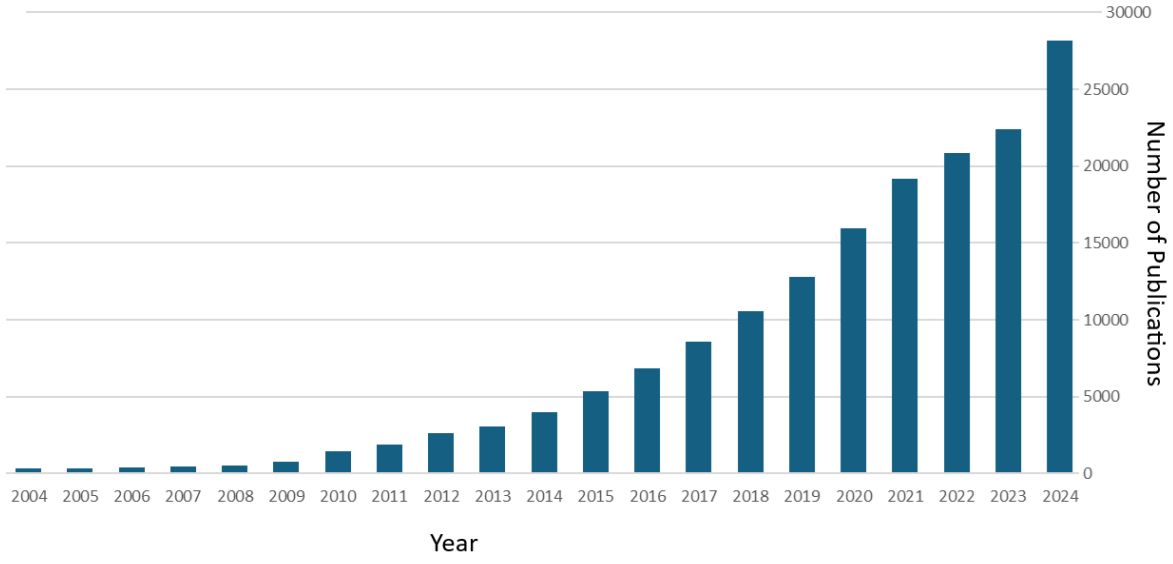

Figure 1: PubMed-derived number of publications including the term theranostic or theragnostic during each year from 2004 to 2024 (search performed February 20, 2025).

A theranostic pair could be either co developed (parallel model) or developed sequentially (in-series model) and each of these pathways will have specific regulatory considerations which need to be taken into account and will be discussed in this thesis.

1.4. Drug Marketing Authorisation Process

Marketing authorisation for drugs is a critical process that ensures that a new medication is safe, effective, and of high quality before it can be made available to the public. According to CFR Title 21 Section 505 §355), no person shall introduce or deliver for introduction into inter-state commerce any new drug, unless an approval of an application. The respective Directive 2001/83/EC of the European Parliament and of the Council prohibits the marketing of unauthorised medicinal products by Article 6(1) stating that no medicinal product shall be placed on the market in the EU unless it has been authorised in accordance with the provisions of the directive.

Ideally marketing authorisations should provide a robust mechanism for patient access to safe and effective drugs. Both, the patient and the future marketing authorisation holder ("MAH") share a great interest in fast approvals to deliver timely benefits to patients in need and in case of the MAH get return for the investment in due course. While the MAH aims to generate profit, the patient and health insurances aim for a low price to make the drug affordable for as many patients as possible. To balance these opposing goals, as well as the above-mentioned aim of safe and effective drugs, the marketing authorisation process needs to find the scale between clear and reliable guidance and tailoring the requirements to the radiopharmaceutical. In the following Chapter, the standard, as well as special requirements and approaches to obtain a marketing authorisation are presented.

Safety

Before a drug can be approved, extensive testing is conducted to assess its safety profile. This includes preclinical studies and clinical trials involving human participants. Regulatory agencies, such as the FDA in the United States or the EMA in Europe, review data on potential side effects, adverse reactions, and overall safety to ensure that the benefits of the drug outweigh any risks. For radiopharmaceuticals specific guidelines regarding the requirements exist (see Chapter 5.1 *Theranostic Aspects in Preclinical Studies*).

Efficacy

As discussed above, benefits and risks related to the use of medicinal products are taken into account when granting a marketing authorisation. Already in 1962 with the Keyfauver Harris Amendment the FDA stating the effectiveness requirement being substantial evidence that the drug will have the effect it purports or is represented to have under proposed labelled conditions of use, the modern regulation of medicines requiring a combination of safety and efficacy came into place. In Europe, the EMA is advocating since her inception in 1995, the assessment of efficacy as a requirement for MA based on clinical studies. A detailed discussion on the clinical trials for theranostic radiopharmaceuticals can be found in Chapter 2.2 *Theoretic Clinical Trial Designs* and Chapter 3 *Clinical Trials for Theranostic Radiopharmaceuticals*.

Quality

Quality assurance is essential in the drug approval process. This involves ensuring that the drug is manufactured consistently and meets specific standards throughout its production. Regulatory agencies require detailed information about the manufacturing process, quality control measures, and stability testing to confirm that the drug will maintain its efficacy and safety over time. For radiopharmaceuticals specific requirements beyond GMP, like radionuclide purity, radiochemical purity, radioactivity, sterility test, endotoxin/pyrogen tests are needed.

This thesis focuses on the clinical view, thus no further discussion on quality requirements and their relevance for the different approval pathways will be discussed.

EU (EMA)

The European Union (EU) offers a range of regulatory pathways for the approval of medicinal products tailored to different types of medicines and specific market needs.

Since the introduction of Regulation 726/2004/EC all human medicines derived from biotechnology and other high-tech processes must be evaluated by the European Medicines Agency (EMA) via the centralised procedure. The same applies to all advanced therapy medicines and medicinal products containing new active substances intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases. For medicines that do not fall under any of the above-mentioned categories, companies can submit an application to the Agency, provided the medicine is a new active

substance, constitutes a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patients at EU level. The Committee for Medicinal Products for Human Use ("CHMP") is the EMAs committee responsible for the scientific evaluation of the application dossier on the quality, efficacy and safety of the medicinal product as part of the centralized marketing authorisation ("MAA") procedure for new drugs. Once granted by the European Commission, the centralised marketing authorisation is valid in all EU and EEA-EFTA states (Iceland, Liechtenstein and Norway).

Products that do not fall under the mandatory scope of the centralised procedure can be authorised via national procedures or via the Decentralised ("DCP") and Mutual Recognition Procedures ("MRP").

The EU approval process is presented in more detail in Annex 2 and 3.

United States of America (FDA)

The FDA has established various pathways for the approval of new drug applications ("NDAs") to ensure that safe and effective medications are available to the public. Among these pathways, sections 505(b)(1) and 505(b)(2) of the Federal Food, Drug, and Cosmetic Act are the most important ones.

Stand-alone applications

The 505(b)(1) pathway is the traditional route for the approval of new drugs. This process requires the submission of a full NDA, including extensive data from preclinical studies and clinical trials to demonstrate the safety and efficacy of the drug for its intended use.

Literature based approvals

Literature-based approvals refer to the process by which the FDA approves a medicinal product based on the review of existing scientific literature, rather than requiring the sponsor to conduct new clinical trials. This approach is typically applied in specific cases and under certain circumstances where adequate evidence already exists in scientific publications. The approval pathway under Section 505(b)(2) allows for a hybrid submission that combines new clinical data with data from published literature or previous findings. This section is particularly relevant for drugs approved based on literature-based evidence.

The US approval process is presented in more detail in Annex 2 and 3.

1.5. Companion Diagnostics

The term “Companion diagnostic” (“CDx”) is often associated with theranostic radiopharmaceuticals [7,8]. According to the NIH dictionary, a CDx is

> “*A test used to help match a patient to a specific drug or therapy. For example, a companion diagnostic test may identify whether a patient’s tumor has a specific gene change or biomarker that is targeted by the drug. This helps determine if the patient should receive the drug or not. Companion diagnostic tests can also be used to find out whether serious side effects may occur from treatment or how well treatment is working. Most drugs with a companion diagnostic test are cancer drugs that target specific tumor mutations.*” [9].

The term “Companion Diagnostics” was first implemented in the EU with the in vitro diagnostic medical device regulation (IVDR) becoming effective in May 2022. Under IVDR, CDx are classified as Class C devices (the second highest risk level) and require conformity assessment by a notified body and a consultation with a medicinal products authority to assess the device's suitability for the related medicinal product.

The FDA defines a companion diagnostic (“CDx”) device to be either an in vitro diagnostic (IVD) device or an imaging tool that provides information which is essential for the safe and effective use of a corresponding therapeutic product. CDx in the US are regulated via the federal Food, Drug, and Cosmetic Act in CFR Title 21 Sub-chapter H Part 809 In vitro diagnostic products for human use. Unlike in the EU with the IVDR, in the US CDx are not legally defined but described in four guidances.

Recently, in January 2024, the Center for Devices and Radiological Health (“CDRH”) announces to begin the reclassification process for most already approved in vitro diagnostics that were traditionally classified as Class III medical devices into Class II (moderate-risk devices). This would enable manufacturers of CDx to seek marketing authorisation through the 510(k) clearance pathway rather than the more rigorous pre-market approval (“PMA”) pathway [10] (for more information see Annex 2). Nevertheless, FDA still applies a risk-based approach to determine the regulatory pathway for IVD CDx devices, as it does with all medical devices. This means that the regulatory pathway will depend on the level of risk to patients, based on the intended use of the IVD CDx device and the controls necessary to provide a reasonable assurance of safety and effectiveness. Thus, the level of risk together with available controls to mitigate risk will establish whether an IVD CDx device requires a PMA or a premarket notification

submission (510(k)) [11]. The mean decision time was reported to be 338 days (median = 309 days) for De Novo requests (with a high variability of 1-30 month), 150 days for 510(k)s and 399 days for PMA devices [12].

Further information on the regulatory framework for CDx in the EU and the US can be found in Annex 2: Marketing Authorisation Process. The use of the term and the regulatory basics of "Companion Diagnostics" in the theranostic approach is discussed in the Chapter 6.3 *Regulatory Frameworks that Feature Linkages between Diagnosis and Therapy*.

1.6. Source and Retrieval of Information

Selection of discussed radiopharmaceuticals

Although the use of the term "theranostic" is relatively recent, the concept goes back to the earliest days of nuclear medicine, when the use of radioiodine for diagnosis and therapy of benign and malignant thyroid disease started. As the regulatory landscape and framework significantly evolved and changed over the last years, this thesis focusses on recent developments in theranostics and thus only discusses the approvals of the last 10 years. Consequently, the theranostic approaches with radioiodine (^{223}Ra -dichloride, first approval 2013) for altered osteogenic activity as well as Zevalin for the treatment of non-Hodgkin lymphoma (first approval 2011) was not included.

Furthermore, Metaiodobenzylguanidin (MIBG) labelled with ^{123}I and ^{131}I, which was introduced into clinical practice in the early 80´s [13] and is now widely employed for the routine diagnostic localization of phaeochromocytomas and neuroblastomas, will not be discussed in this thesis. Although AZEDRA® (I-131 MIBG), indicated for the treatment of adult and pediatric patients 12 years and older, with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy was approved in 2018, the diagnostic use of I-131 MIBG was already approved by the FDA in 1994. Furthermore, the diagnostic radiopharmaceutical Adreview® (I-123-MIBG) was approved in the US in 2008 (no approval in the EU) and thus marketed more than 10 years ago and consequently not discussed in this thesis.

To date, all approved therapeutic radiopharmaceuticals in theranostic use are intended for the treatment of cancer [3], thus in EU all new therapeutic radiopharmaceuticals fall under

the mandatory scope of centralised procedure (for further explanation on marketing authorisation procedures see Annex 2). Although diagnostic radiopharmaceuticals only fall under the mandatory scope of centralised procedure if they are intended for rare diseases, only a few radiopharmaceutical generics like Illuccix® [14] (PSMA-11) and [^{18}F]PSMA-1007 [15] have been approved on a national level in the last years. In this thesis for the EU only the centralised procedure and its features will be discussed.

In summary, as also shown in Figure 3: The Current Status of Global Theranostics in 2024 (Source: Oppenheimer & Co. Research), Lutathera® and Pluvicto® as approved therapeutic compounds together with the associated diagnostic radiopharmaceuticals as well as theranostic compounds in development (selection based on Figure 3) will be considered in this thesis.

Retrieval of information on approved radiopharmaceuticals:

Regulatory information on the FDA-approved radiopharmaceuticals have been retrieved via Drugs@FDA, the Drug Database of the FDA [16]. Letters, Labels, prescribing information (PI) and Review information are provided in this database up-to-date for all drugs approved by the FDA.

Regulatory information on the radiopharmaceuticals approved in the EU was retrieved from EPARs (European Public Assessment Report) [17], SmPcs (Summary of product characteristics), assessment history and further information published for every human or veterinary medicine application that has been granted or refused a marketing authorisation.

Retrieval of information on clinical studies

Information on clinical studies was extracted from clinicaltrials.gov [18]. Clinicaltrials.gov is a US government database where clinical studies can be registered. As registration is required by US law [42 CFR Part 11] for all controlled drug clinical investigation, clinicaltrials.gov, the world's largest public clinical trials registry is a comprehensive repository. Information provided include among others the trial protocol, the statistical analysis plan and the administrative information. Furthermore, information on clinical trials have been retrieved from Drugs@FDA and the European EPARs, which can be found on the EMA webpage.

Retrieval of information on theranostic radiopharmaceuticals under development and the respective ongoing clinical trials

The selection of radiopharmaceuticals under development discussed in this Chapter and thereafter is based on a publication in 2024 from Oppenheimer & Co. Research discussing the current landscape of theranostics (Figure 3). Information on clinical trials were extracted from clinicaltrials.gov [18].

2. Theoretic Theranostic Approach

This Chapter will lay the foundation for understanding the subsequent discussion on the best development and approval pathway for theranostic radiopharmaceuticals. The theoretic concepts of theranostic development and approval will be discussed following the chronological sequence of drug development from preclinical studies to approval.

2.1. Preclinical Requirements for Theranostic Radiopharmaceuticals

According to the EMA Guideline on Clinical Evaluation of diagnostic agents [19], which is applicable for diagnostic radiopharmaceuticals, clinical development programs with respect to quality, pharmacology, toxicology, pharmacokinetics and safety should be adapted for diagnostic drugs used to diagnose and/or monitor diseases/conditions and not for treatment. One of these adjustments is the concept of microdosing, which is also established in the US.

Microdosing approach

For diagnostic radiopharmaceuticals, usually applied in doses less than 100 µg, the concept of microdosing applies. Based on the assumption that these diagnostic drugs are administered using a dose at the low end of the dose-response curve where dose-related adverse events are unlikely to occur, only a limited number of preclinical safety studies are required [20]. For therapeutic radiopharmaceuticals in the field of oncology the FDA guidance on Microdose Radiopharmaceutical Diagnostic Drugs [20] defines the needed preclinical studies. A comparison of the requirements can be found in Table 1: Preclinical requirements for radiopharmaceuticals (FDA).

FDA	**Diagnostic Radiopharmaceutical (Microdose)** [20]	**Therapeutic Radiopharmaceutical [Cancer]** [21]
Primary pharmacology	in vivo and in vitro pharmacologic characterizations	target binding and antitumor activity
Safety pharmacology	Not needed	incorporated into the design of toxicology and/or animal biodistribution studies
Animal biodistribution and dosimetry	Pharmacokinetic & in vitro biochemical information	single dose administration in a single animal species (incl. pharmacokinetics)

Toxicology	Extended single-dose toxicity in one species with cold radiopharmaceutical	- Evaluation of ligand-induced toxicity with the cold pharmaceutical in one species - Long-Term ligand- and radiation-related toxicities assessments to support Marketing [exemptions possible]
Genotoxicity, Reproductive Toxicology, Carcinogenicity Studies	Not needed	

Table 1: Preclinical requirements for radiopharmaceuticals (FDA)

In the EU the guideline on the non-clinical requirements for radiopharmaceuticals [22] is in draft since 2018, no final version has been published yet. In the draft version the agency distinguished rather between microdose and doses above microdose than between therapeutic and diagnostic compounds (see Table 2). Radiation induced toxicity is regulated via the Directives of EURATOM (Directive 2013/59/Euratom).

EMA	**Microdose Radiopharmaceutical** [22]	**Single sub-pharmacological (but above microdose) or pharmacologically active doses** [22]
Primary pharmacology	In vitro target/receptor profiling to show pharmacological activity of the non-radioactive part or its absence	
Safety pharmacology	Not needed	standard core battery
animal biodistribution and dosimetry	In vivo stability, distribution and elimination to allow estimation of tissue and whole-body radiation doses for therapeutics: dosimetry in animal model of disease	
Toxicology	extended single dose toxicity studies a rodent	extended single dose toxicity studies in a rodent (and non-rodent)
Genotoxicity, Reproductive Toxicology, Carcinogenicity Studies	Not recommended	Testing of the non-radioactive part for genotoxicity

Table 2: Preclinical requirements for radiopharmaceuticals (EMA)

Both, the FDA and the EMA acknowledged that radiopharmaceuticals are diagnostic imaging agents with unique characteristics and that high development costs might prevent the development of new drugs. Thus, in the last years several facilitations were introduced and requirements were harmonized between the agencies [23].

Theranostics with same ligands for therapeutic and diagnostic part

Although the toxicological requirements would be similar for diagnostic and therapeutic compound with same ligand, minor chemical changes in a peptide can fundamentally alter its binding affinities. For example, the somatostatin receptor antagonist DOTA-JR11 has a more than 10-fold lower binding affinity when labeled with ^{68}Ga compared to the case when it is labeled with ^{177}Lu. Consequently, the combination of [^{68}Ga]Ga-DOTA-JR11/[^{177}Lu]Lu-DOTA-JR11 is not an ideal theranostic pair [24].

2.2. Theoretic Clinical Trial Designs

Diagnostic radiopharmaceuticals

Typically, a diagnostic medicinal product, depending on its clinical context, seeks one of the below four indications [25]:

- Structure delineation
- Disease or pathology detection or assessment
- Functional, physiological, or biochemical assessment
- Diagnostic or therapeutic clinical management

While structure delineation is rather the strength of imaging technologies like MRI and CT, diagnostic radiopharmaceuticals have its strength in functional, physiological, or biochemical assessment and the subsequent disease or pathology detection or assessment, as well as the clinical management which results from obtained information. In the concept of theranostic radiopharmaceuticals, especially the impact of the diagnostic drug on the therapeutic clinical management is of interest. To assess this impact, distinguishing between predictive and prognostic radiopharmaceuticals is of high importance. This was in detail described by Wang et al. [26] and will be summarized based on this publication under the next headings.

Predictive diagnostic radiopharmaceuticals (treatment effect)

Unlike traditional diagnostic tools that provide a snapshot of current conditions (e.g., X-rays or CT scans), predictive radiopharmaceuticals can offer insight into the treatment response.

When the molecular target truly predicts the treatment response, an extreme scenario can be constructed in which patients lacking the molecular target show no treatment effect. Thus, the benefit of a trial design, using a theranostic approach to select patients with the molecular

target and only assess the treatment effect in those, can be significant if the molecular target is proven to predict the treatment response. In this case, a theranostic approach protects patients without expression of the target by avoiding an "ineffective" treatment in these cohort. Summarized, predictive diagnostic radiopharmaceutical help to identify subpopulations of an indication which likely are more responsive to the associated therapeutic radiopharmaceutical.

However, in many cases, the assumption that the molecular target predicts the treatment effect is based on a theoretic mechanistic hypothesis and not or only partly shown during a clinical trial. Consequently, the associated diagnostic drug may not always accurately predict the effectiveness of a molecularly targeted therapy in reality. This could be due to an incomplete understanding of the therapeutic mechanism or limitations in the diagnostic test. However, even if the presumed predictive molecular targeting does not reflect the actual biological situation, targeting patients based on their baseline characteristics or biomarkers may still be valuable for enhancing prognosis in a properly designed and controlled clinical trial [26]. These prognostic radiopharmaceuticals are discussed in the following section.

Prognostic diagnostic radiopharmaceuticals (disease or disease outcome)

Prognostic diagnostic radiopharmaceuticals are used to assess the outcome or future course of a disease in a patient. Unlike predictive radiopharmaceuticals, which focus on predicting whether a treatment is likely to succeed or fail, prognostic radiopharmaceuticals are designed to give an indication of how a disease will progress or what the likelihood of recovery or complications might be [26].

These radiopharmaceuticals are typically used to estimate the long-term outcome of a disease and guide clinical decision-making. They can be essential for personalized medicine, as they provide insights into individual disease behaviour and treatment efficacy, helping healthcare providers tailor interventions. Of note, the FDA highlights that "*Studies using prognostic enrichment as a selection or study entrance criteria have been accepted as a basis of drug approval for marketing without a requirement to study broader populations*" [26].

In summary, prognostic diagnostic radiopharmaceutical can predict the outcome of a disease, for example a better or a worse overall survival of the patient.

Prognostic-predictive diagnostic radiopharmaceuticals

Prognostic-Predictive diagnostic radiopharmaceuticals combine both prognostic and predictive capabilities. These drugs are designed to provide diagnostic information that can not only help in understanding the likely progression of a disease (prognosis) but also predict the response to treatment (predictive), helping clinicians make informed decisions about treatment strategies, potential interventions, and long-term care.

Theranostic trial design combining evaluation of the therapeutic and the diagnostic compound

In-Parallel with Leveraging framework

As described by an employee of the FDA [25], the development of the "nostic" part of a theranostic pair can be performed in-parallel with the therapeutic development. Using this parallel approach design efficacy can potentially be increased through leveraging. Using imaging sub-trials, the technical and diagnostic performance of the diagnostic radiopharmaceutical can be assessed in the definitive therapeutic trial samples. This presents direct assessment opportunity of the same patients as for the therapeutic study. Contrarily to the below discussed concentration on patient selection performance, this approach allows for an independent approval of the diagnostic radiopharmaceutical.

Sample size savings by using the predictive value of the diagnostic radiopharmaceutical

If the molecular target is known to predict the effect of a treatment, the efficiency of the therapeutic trial design can be improved by selecting patients using the diagnostic radiopharmaceutical. Using this approach only the treatment effect in patients for which the molecular target is known to be prevalent is investigated. Based on the prevalence of the molecular target this can markedly decrease the sample size needed as patients without treatment effect are excluded prior to the therapeutic intervention (see Figure 2).

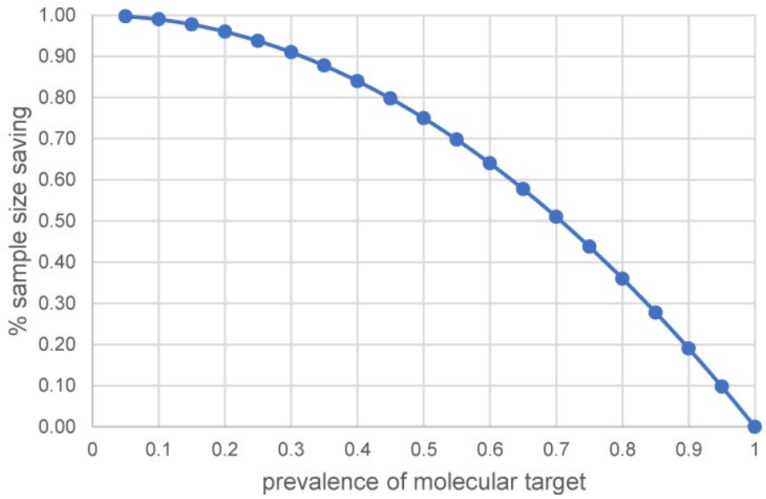

Figure 2: % of sample size saving for predictive diagnostic radiopharmaceuticals (Source: Wang et al. 2022 *[26]*)

Prognostic enrichment using the prognostic value of the diagnostic radiopharmaceutical

Diagnostic radiopharmaceuticals with prognostic value can be used to select patients with a more severe course of the disease or a greater likelihood of reaching specific trial endpoints. Even though with a purely prognostic diagnostic radiopharmaceutical there is strictly speaking, no sample size saving as all patients are studied, prognostic enrichment can increase the study power resulting in a higher probability of identifying a favourable treatment effect, if it exists, compared to studying unselected patients without employing an enrichment strategy [26].

Of note, this purely prognostic value is rarely seen and usually the molecular target possesses the characteristic of being both prognostic of disease state and predictive of differential treatment effects [26].

2.3. Theoretic Approval Pathways for Theranostics

Reliance on available diagnostic radiopharmaceutical

The reliance on an available diagnostic radiopharmaceutical (also called sequential paradigm [25]) requires a diagnostic radiopharmaceutical to be approved prior to the evaluation of the therapeutic radiopharmaceutical. This diagnostic radiopharmaceutical was developed independent of the theranostic development and usually there is no mention about patient

selection in its indication statement. An example for this approach is Octreo-Scan®-Lutathera® theranostics with OctreoScan® being approved about 25 years prior to Lutathera®.

Diagnostic approval first

As the requirements and needed data for diagnostic radiopharmaceuticals, often administered in a micro-dose level, are lower compared to therapeutic radiopharmaceuticals, the development is often faster. Thus, approval of the diagnostic radiopharmaceutical, given that the clinical trials were designed to show a prognostic or predictive-prognostic capability, can be obtained independent from the therapeutic radiopharmaceutical. This approach is currently the most used one. An example is the development of the theranostic pair ^{68}Ga-/^{177}Lu-DOTATATE by Advanced Accelerator Applications.

Parallel development and approval

As already described in the section on Clinical Trial Designs in the introduction, the value of diagnostic radiopharmaceuticals can lay solely in the prediction of the treatment effect of a therapeutic compound with no intention to develop as a traditional diagnostic radiopharmaceutical. Nevertheless, these radiopharmaceuticals are investigational, therefore, regulatory approval for the diagnostic part is necessary [25]. Consequently, a parallel development might be of use as it allows a targeted approach to optimize the theranostic pair. A theoretic approach to optimize a parallel development of a radio-theranostic and its diagnostic counterpart has been described by Wang et al. 2020 [25]. The above discussed “In-Parallel with Leveraging” development pathway for Theranostic drug approvals, includes imaging design elements, imaging baseline factors, imaging biomarkers and imaging endpoints into therapeutic trials. This allows for a simultaneous development and thus potentially reduces combined development time by planning an imaging sub-trial within a Phase 3 therapeutic trial following patient consent for tissue confirmation. An example for a parallel development is the theranostic pair Locametz® and Pluvicto®. Further discussions on the realization of the parallel development can be found in Chapter 5 *Evaluation of Theranostic Aspects*.

Therapeutic approval first

A scenario is also conceivable in which a new diagnostic radiopharmaceutical is used together with an already approved theranostic radiopharmaceutical. The approval of this new diagnostic radiopharmaceutical might be driven by lower costs, improved safety profile, better availability or better technical or diagnostic performance. An example for a diagnostic radiopharmaceutical which was developed and approved after the therapeutic radiopharmaceutical is ^{18}F-Flotufolastat (Posluma®) or [^{64}Cu]Cu-DOTATATE (DETECTNET®).

3. Clinical Trials for Theranostic Radiopharmaceuticals

In this Chapter, the pivotal clinical trials for diagnostic and therapeutic radiopharmaceuticals in theranostic use will be evaluated. Marketed radiopharmaceuticals and radiopharmaceuticals under development will be evaluated with the aim to analyse whether theranostic clinical trials have already been implemented or standard stand-alone diagnostic or therapeutic trials are still dominant.

EU and US approvals often share international clinical trials. From a theranostic point of view, the pivotal clinical trials for the somatostatin agonists do not overlap, while two of the PSMA ligands share pivotal clinical trials, namely [^{68}Ga]Ga-PSMA-11 (Locametz®) and [^{177}Lu]Lu-PSMA-617 (Pluvicto®). This theranostic pair of radiopharmaceuticals both use the PSMA-617-01 (VISION) trial for the EU MAA as well as for the US NDA.

As discussed in Chapter 2 Section *Theoretic clinical trial design for diagnostic radiopharmaceuticals*, such trials can, if designed correctly, not only reduce patient numbers by combining investigations for two products but also even further by using a leverage concept to select the suited patients for the treatment. This is further discussed in Chapter 5.2 *Theranostic Aspects in Clinical Trials*.

Although usually two pivotal Phase 3 trials are required [27] for drug approval, most radiopharmaceuticals received approval with only one Phase 3 trial. Only the recent approvals of ^{18}F-Piflufolastat (PYLARIFY® in the EU resp. PYLCLARI® in the US) and Posluma® in the EU provided two Phase 3 trials for approval. The number of patients imaged resp. treated in the pivotal trials vary between less than 200 for the literature-based approvals of the diagnostic radiopharmaceuticals [^{64}Cu]Cu-DOTATATE (DETECTNET®) or [^{68}Ga]Ga-DOTATATE (NetSpot®) to more than 100 patients for the therapeutic radiopharmaceuticals [^{177}Lu]Lu-DOTATATE (Lutathera®) and [^{177}Lu]Lu -PSMA-617 (Pluvicto®).

While some of the later MAHs also conducted the clinical trials, for several of the approved radiopharmaceuticals, MAH and trial sponsor are different. Furthermore, pivotal data was also taken from literature.

3.1. Pivotal Clinical Trials submitted for Efficacy and Safety of granted Approvals

EU approvals

	Phase	Trial name	Patient No	Trial Sponsor	Comments	MAH
GEP-NETs						
[^{68}Ga]Ga-DOTATOC (SomaKit TOC®)	Listing of 31 publications		970	various	---	Advanced Accelerator Applications (AAA, Novartis)
	Meta-analyis of 12 publications		386	various	---	
[^{177}Lu]Lu-DOTATATE (Lutathera®)	I/II	Erasmus MC	1214	Erasmus MC	MEC127.545/1993/84	AAA (Novartis)
	III	NETTER-1	116	AAA	EudraCT/IND: AAA-III-01 (2011-005049-11/77219)	
PSMA positive prostate cancer						
^{18}F-Piflufolastat (PYLCLARI®)	II/III	OSPREY	385	Progenics Pharmaceuticals	NCT02981368	Curium
	III	CONDOR	208	Progenics Pharmaceuticals	NCT03739684	
	III	PYTHON	205	Curium	EudraCT: 2020-000121-37	
[^{68}Ga]Ga-PSMA-11 (Locametz®)	III	PSMA-617-01 (VISION)	831	AAA	NCT03511664	AAA (Novartis)
	reviewer variability study based on VISION trial		70	AAA	---	
	Dosimetry calculations based on one publication		6	Sandgren et al. (2019)	---	
[^{177}Lu]Lu-PSMA-617 (Pluvicto®)	III	PSMA-617-01 (VISION)	831	AAA	NCT03511664	Novartis
	II	RESIST-PC Trial (PSMA-617-02)	64	Endocyte (Novartis)	NCT03042312	

AAA: Advanced Accelerator Applications, Erasmus MC: Erasmus Medical Center, GEP-NET: Gastroenteropancreatic neuroendocrine tumors; MAH: Marketing Authorisation Holder

Table 3: Overview of clinical trials submitted for EMA approval of theranostic radiopharmaceuticals

US approvals

	Phase	Trial name	Patient/ Controls No	Sponsor	Comments	MAH
GEP-NETs						
[^{68}Ga]Ga-DOTATATE (NetSpot®)	I/II	A (VUMC study)	97	Vanderbilt University Medical Center	---	Advanced Accelerator Applications (AAA, Novartis)
	retrospective	B (Haug et al 2012)	104	LMU Munich	---	
	retrospective	C (Haug et al 2014)	63	LMU Munich	---	
[^{68}Ga]Ga-DOTATOC	Retrospective of three I/II prosp. studies	RET-NET-01	220 + 62 + 52	University of Iowa, National Cancer Institute	NCT01619865 + NCT 01869725 + NCT2441062	University Iowa
	Meta-analysis of 17 paper	GRAHAM-2017	---	University of Iowa	---	
[^{64}Cu]Cu-DOTATATE (DETECTNET®)	III	RMX-18-22	42 patients + 21 healthy	Radiomedix	Single center, no NCT available	Radiomedix
	literature-based retrospective analysis	NETMedix Denmark Trial	112	Pfeifer et al., 2015[28]	Single center	
[^{177}Lu]Lu -DOTATATE (Lutathera®)	III	NETTER-1	229	AAA	EudraCT/IND: AAA-III-01 (2011-005049-11/77219)	AAA (Novartis)
	I/II	Erasmus MC	1214	Erasmus Rotterdam	MEC127.545/1993/84	
PSMA positive prostate cancer						
[^{68}Ga]Ga-PSMA-11 (Locametz®)	II	PSMA-PreRP	325	UCSF/UCLA	NCT03368547 and NCT02919111	AAA (Novartis)

	II	PSMA-BCR	635	UCSF/UCLA	NCT02940262 and NCT02918357	
	III	VISION trial	1003	AAA	NCT03511664	
[^{68}Ga]Ga-PSMA-11	II	PSMA-PreRP	325	UCSF/UCLA	NCT03368547 and NCT02919111	UCSF/UCLA
	II	PSMA-BCR	635	UCSF/UCLA	NCT02940262 and NCT02918357	
^{18}F-flotufolastat (Posluma®)	III	BED-PSMA-301 (LIGHTHOUSE)	356	Blue Earth Diagnostics	NCT04186819	Blue Earth Diagnostics
	III	BED-PSMA-301 (SPOTLIGHT)	391	Blue Earth Diagnostics	NCT04186845	
^{18}F-Piflufolastat (PYLARIFY®)	III	OSPREY	385	Progenics Pharmaceuticals	NCT02981368	Progenics Pharmaceuticals
	III	CONDOR	208	Progenics Pharmaceuticals	NCT03739684	
[^{68}Ga]Ga-PSMA-11 Illuccix®	II	PSMA-PreRP	325	UCSF/UCLA	NCT03368547 and NCT02919111	Telix
	II	PSMA-BCR	635	UCSF/UCLA	NCT02940262 and NCT02918357	
[^{177}Lu]Lu-PSMA-617 (Pluvicto®)	III	VISION trial	831	AAA	NCT03511664	AAA (Novartis)
	II	PSMA-617-02 (RESIST-PC)	64	Endocyte (Novartis)	NCT03042312	
	II	TheraP	201	Australian and New Zealand Urogenital and Prostate Cancer Trials Group	NCT03392428	

AAA: Advanced Accelerator Applications; Erasmus MC: Erasmus Medical Center, Rotterdam; GEP-NET: Gastroenteropancreatic neuroendocrine tumors; LMU: Ludwig-Maximilians-Universität; MAH: Marketing Authorisation Holder; UCSF: University of California San Francisco; UCLA: University of California, Los Angeles

Table 4: Overview of clinical trials submitted for FDA approval of theranostic radiopharmaceuticals

3.2. Ongoing Clinical Trials for Theranostic Radiopharmaceuticals under Development

As shown in Figure 3, several companies are currently developing theranostic radiopharmaceuticals. Of note this high number of radiopharmaceuticals in clinical trials is misleading in regard to the number of new active ingredients and new theranostic pairs of radiopharmaceuticals. As listed in Annex 5, several of the compounds, in the figure named with their proprietary name, are generics of the already approved radiopharmaceuticals (PNT2003) or build upon existing diagnostic radiopharmaceuticals (ITM-11 = [^{177}Lu]Lu-DOTATOC or RYZ101 = ^{225}Ac-DOTATATE, Alphamedix = ^{212}Pb-DOTAMTATE, TLX591, ^{225}Ac-FL-020, CONV01-α). Furthermore, also therapeutic radiopharmaceuticals without a diagnostic counterpart are named here (Iomab-B, LNTH-1095), which according to the definition in section Theranostic Approach are not in scope of this thesis. Yet others, however, clinical trials were recently terminated pointing towards a stop of development for these theranostics (FF58). Finally, for some of the therapeutic radiopharmaceuticals no patent was filed (PSMA I&T = PNT2002 = FPI-2265) and thus several companies are working on developing these compounds in parallel [29].

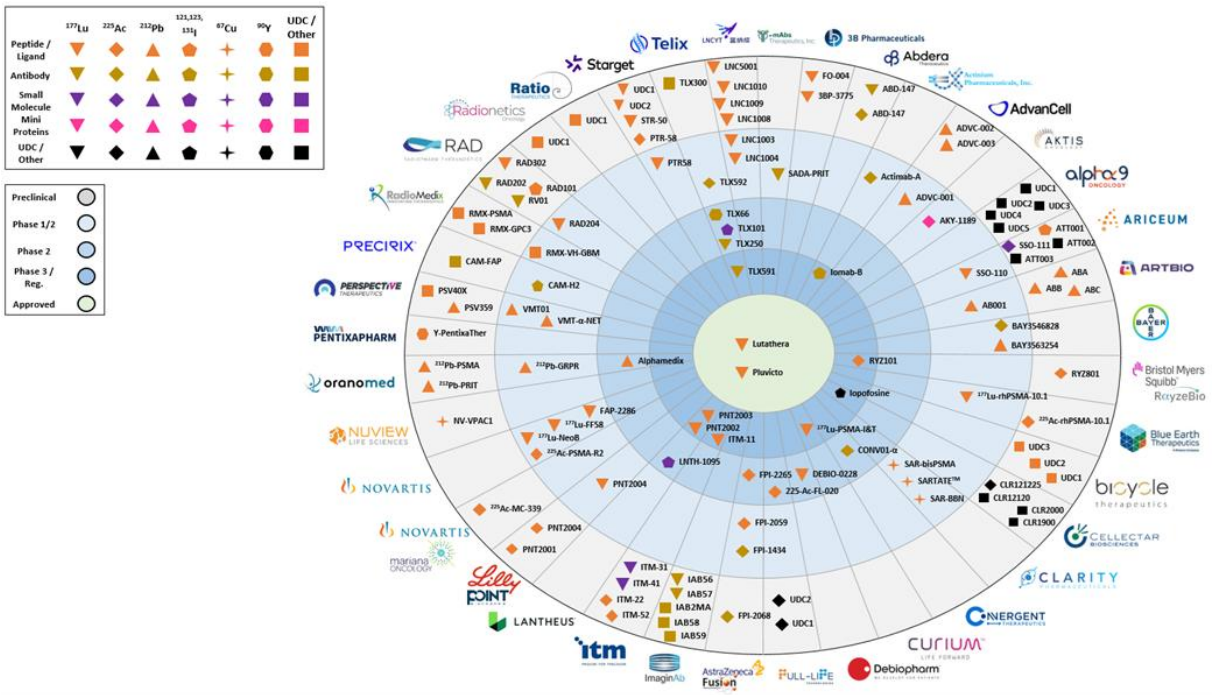

Figure 3: The Current Status of Global Theranostics in 2024 (Source: Oppenheimer & Co. Research)

In summary most of the above-described radiotherapeutics (Figure 3) target structures which a) are already covered by the approved theranostic compounds and thus use the already available diagnostic radiopharmaceuticals or b) do not include a diagnostic part and have thus no need for a theranostic approval pathway. Nevertheless, there are some compounds under development exploring new theranostic targets. In Annex 3, Table 20 the theranostic pairs with the therapeutic part at least advanced to a Phase II status are listed and three examples are discussed below.

Debio 0228 ([^{177}Lu]Lu-DPI-4452) / Debio 0328 ([^{68}Ga]Ga-DPI-4452)

Debio 0228/0328 is targeting the Carbonic Anhydrase IX (CA IX) surface protein. CA IX plays a key role in the tumor microenvironment, promoting tumor growth, survival, invasion and metastasis. The theranostic pair is currently being evaluated in the phase 1/2 GaLuCi™ clinical trial for Clear Cell Renal Cell Carcinoma, Pancreatic Ductal Adenocarcinoma and Colorectal Cancer.

This theranostic trial is being carried out in three stages. The ongoing Part A is evaluating the safety and performance of the imaging drug in detecting CA IX-expressing solid tumors. Part B will assess escalating doses of the therapeutic drug, ITM-91 (Debio 0228) in patients, whose tumors show high uptake of imaging tracer. Finally, based on the recommended dose from Part B, Part C of the trial will further assess the safety and preliminary efficacy of ITM-91 (Debio 0228) in Clear Cell Renal Cell Carcinoma, Pancreatic Ductal Adenocarcinoma and Colorectal Cancer.

The trial design of the phase 1/2 GaLuCi™ clinical trial clearly acknowledges the theranostic approach by combining the needed safety assessments for both radiopharmaceuticals. No further trials on these two compounds are currently ongoing. Thus, a parallel development and approval (see Chapter 2) can be emphasized. It remains to be seen whether the theranostic concept will also be applied to Phase III trials.

[^{177}Lu]Lu- and [^{68}Ga]Ga-FAP2286

Fibroblast activation protein (FAP) is a cell surface protein that is highly expressed on the surface of cancer-associated fibroblasts present in the tumor microenvironment of most epithelial cancers, whereas limited expression of FAP is observed in normal tissues. Thus, it is a

promising target for peptide-targeted radionuclide imaging and therapeutic drugs. End of 2020 Clovis Oncology submitted two Investigational New Drug Applications ("INDs") for this novel peptide-Targeted radionuclide for Therapeutic and Imaging Clinical Trial. The subsequently followed Phase I/II trial in Advanced Solid Tumors (LuMIERE) started in July 2021. Phase 1 of this trial is designed to evaluate the safety and establish the recommended intravenous Phase 2 dose for [^{177}Lu]Lu-FAP2286 monotherapy in participants with FAP expressing solid tumors. Phase 2 is designed to evaluate the safety and efficacy of [^{177}Lu]Lu-FAP2286 as monotherapy in participants. Participants in both Phase 1 and 2 will be selected for treatment with [^{177}Lu]Lu-FAP2286 based on [^{68}Ga]Ga-FAP2286 imaging for determining tumor FAP expression.[30] In contrast to the above-described DPI-4452 trial, synergies which might be used for theranostic pairs of radiopharmaceuticals are not fully utilized for FAP2286. Although [^{68}Ga]Ga-FAP2286 is included in the trial, only secondary outcome measures (Comparison of SUV_{max} in tumor lesions and to evaluate the safety and tolerability) are evaluated.

There are two other Phase I trials ongoing which evaluate the diagnostic radiopharmaceutical. Thus, it is unclear whether the company aims for a parallel development and approval or a diagnostic approval first (see section 2.3 *Theoretic approval pathways for theranostics*).

[^{225}Ac]-FPI-1434 and [^{111}In]-FPI-1547

FPI-1434 resp. FPI-1547 is targeting the insulin-like growth factor 1 (IGF-1) receptor, a protein found on the surface of human cells. IGF-1 has an important role in promotion of cell proliferation and inhibition of apoptosis and is thus related to oncogenic transformation, growth and survival of cancer cells [31]. 2019 Fusion Pharmaceuticals started a Phase I/II clinical trial on the therapeutic radiopharmaceutical [^{225}Ac]-FPI-1434 and its related SPECT diagnostic [^{111}In]-FPI-1547. In the trial NCT03746431, dose escalation for [^{225}Ac]-FPI-1434 is combined with a cold antibody sub-study to evaluate [^{225}Ac]-FPI-1434 and [^{111}In]-FPI-1547 in combination with FPI-1175.

Summarizing Chapter 3, with a first example of a theranostic pair (Locametz®/Pluvicto®) being approved based on a theranostic trial, further new theranostic radiopharmaceuticals under development use dedicated trial designs to study the diagnostic and the therapeutic

radiopharmaceutical using leveraging effects. Still, all of these ongoing theranostic trials are Phase I/II trials and thus it remains open whether the theranostic approach to clinical trials will be fully employed for these drug pairs.

4. Approval Pathways of Marketed Theranostic Radiopharmaceuticals

In this Chapter, the approval pathways for marketed diagnostic and therapeutic radiopharmaceuticals in theranostic use will be described. With the aim to compare theranostic approval pathways with standard stand-alone approvals, the legal basis as well as the timing and extent of the submission will be evaluated.

4.1. Approval Pathways EU

As introduced in Annex 2, the EMA offers 7 ways to obtain a centralised marketing authorisation. The here described theranostic radiopharmaceuticals have been either authorised via the standard MA following Article 8(3) or in the case of [^{68}Ga]Ga-DOTATOC via the well-established use pathway following Article 10(a).

Diagnostic radiopharmaceutical	**Approval pathway diagnostic** (Directive 2001/83/EC)	**Approval year**	**Therapeutic radiopharmaceutical**	**Approval pathway therapeutic** (Directive 2001/83/EC)	**Approval year**
GEP-NETs					
[^{68}Ga]Ga-DOTATOC (SomaKit TOC®)	Article 10(a)	2016	[^{177}Lu]Lu-DOTATATE (Lutathera®)	Article 8.3	2017
PSMA positive prostate cancer					
[^{68}Ga]Ga-Gozetotid (Locametz®)	Article 8.3	2022	[^{177}Lu]Lu-PSMA-617 (Pluvicto®)	Article 8.3	2022
^{18}F-Piflufolastat (PYLCLARI®)	Article 8.3	2023			

GEP-NET: Gastroenteropancreatic neuroendocrine tumors

Table 5: Centralised approval pathways for theranostic radiopharmaceuticals EU

Approval and Development Timelines EU

	First in Human	**MAA Submission**	**MAA Approval**	**MAA Review [days]**	**Total development [years]**
GEP-NETs					
[^{68}Ga]Ga-DOTATOC (SomaKit TOC®)	2001 [32]	08.10.2015	13.10.2016	370	15
[^{177}Lu]Lu-DOTATATE (Lutathera®)	2000 [33]	26.04.2016	20.07.2017	451	17
PSMA positive prostate cancer					

[^{68}Ga]Ga-Gozetotid (Locametz®)	2011 [29]	30.09.2021	13.10.2022	379	11
[^{177}Lu]Lu-PSMA-617 (Pluvicto®)	2014 [34]	30.09.2021	13.10.2022	379	8
^{18}F-Piflufolastat (PYLCLARI®)	04/2015 [35]	24.06.2022	25.05.2023	335	8

GEP-NET: Gastroenteropancreatic neuroendocrine tumors, MAA: Marketing Authorisation Application

Table 6: Approval and development timelines of theranostic radiopharmaceuticals (EMA)

4.2. Approval Pathways US

Diagnostic radiopharmaceutical	Approval pathway diagnostic	Approval year	Therapeutic radiopharmaceutical	Approval pathway therapeutic	Approval year
GEP-NETs					
[^{68}Ga]Ga-DOTATATE (NETSPOT®)	505(b)(2) (0 pivotal studies)	2016	[^{177}Lu]Lu-DOTATATE (LUTATHERA®)	505(b)(1)	2018
[^{68}Ga]Ga-DOTATOC (UIHC)	505(b)(2) (2 single center studies)	2019	[^{177}Lu]Lu-DOTATATE	ANDA (under evaluation since 01/24)	---
[^{64}Cu]Cu-DOTATATE (DETECTNET®)	505(b)(2) (1 pivotal trial)	2020			
PSMA positive prostate cancer					
^{68}Ga-PSMA-11 (UCSF)	505(b)(2) (2 pivotal trials)	2020	[^{177}Lu]Lu-PSMA-617 (Pluvicto®)	505(b)(1)	2022
[^{68}Ga]Ga-PSMA-11 (UCLA)	505(b)(2) (2 pivotal trials)	2020			
^{18}F-piflufolastat (PYLARIFY®)	505(b)(1)	2021			
[^{68}Ga]Ga-PSMA-11 (Illuccix®)	505(b)(2) (0 pivotal studies)	2021			
[^{68}Ga]Ga-PSMA-11 (Locametz®)	505(b)(2) (1 pivotal trial)	2022			
^{18}F-flotufolastat (Posluma®)	505(b)(1)	2023			

ANDA: Abbreviated New Drug Application; GEP-NET: Gastroenteropancreatic neuroendocrine tumors

Table 7: Approval Pathways of theranostic radiopharmaceuticals (FDA)

Approval and Development Timelines US

	First in human published	NDA Submission	NDA Approval	Review [days]	Total development [years]
GEP-NETs					
[^{68}Ga]Ga-DOTATATE (NETSPOT®)	2006 [36]	01.07.2015	01.06.2016	336	10
[^{68}Ga]Ga-DOTATOC	2001 [32]	23.05.2018	21.08.2019	455	18
[^{64}Cu]Cu-DOTATATE (DETECTNET®)	2012 [37]	08.07.2019 03.01.2020 (rolling review	03.09.2020	423/244	8
[^{177}Lu]Lu-DOTATATE (LUTATHERA®)	2000 [33]	28.04.2016 26.07.2017 (amendment)	26.01.2018	639	18
PSMA positive prostate cancer					
[^{68}Ga]Ga-PSMA-11	2011 [29]	06.09.2019	01.12.2020	452	9
^{18}F-Piflufolastat (PYLARIFY®)	04/2015 [35]	29.09.2020	26.05.2021	239	6
[^{68}Ga]Ga-PSMA-11 (Illuccix®)	2011 [29]	23.09.2020	17.12.2021	450	10
^{18}F-Flotufolastat (Posluma®)	06/2019 [38]	25.05.2022	25.05.2023	365	4
[^{68}Ga]Ga-PSMA-11 (Locametz®)	2011 [29]	31.07.2021	23.03.2022	235	11
[^{177}Lu]Lu-PSMA-617 (Pluvicto®)	2014 [34]	29.07.2021	23.03.2022	237	8

GEP-NET: Gastroenteropancreatic neuroendocrine tumors; NDA: New drug application

Table 8: Approval and development timelines of theranostic radiopharmaceuticals (FDA)

4.3. Comparison of Approval Pathways

The EU approval pathways of radiopharmaceuticals are quite comparable. The approval via the well-established used pathway took as long as the standard approvals via a full mixed dossier (mean review time: 383 days). Only one radiopharmaceutical, Lutathera®, received an accelerated assessment designation (see Annex 4). Nevertheless, due to a complete response letter, the approval of Lutathera® took longer compared to the other radiopharmaceuticals.

The FDA approvals show a greater variety of designations and pathways. Especially the diagnostic and therapeutic radiopharmaceuticals for GEP-NETs were supported by fast track and frequent priority and rolling review. Only [^{68}Ga]Ga-DOTATOC received none of the acceleration measures. Consequently, the review time of [^{68}Ga]Ga-DOTATOC was slightly longer than the review time of the other diagnostic radiopharmaceuticals targeting GEP-NETs (455 days vs. 336

resp. 423 days). For radiopharmaceuticals targeting PSMA positive prostate cancer the standard review process was usually applied. Only PYLARIFY® and Pluvicto® received a priority review (see Annex 4). Furthermore, no fast track or rolling review was granted. Only the therapeutic compound Pluvicto® received break-through therapy designation. In the case of radiopharmaceuticals targeting PSMA positive prostate cancer the above-mentioned designations significantly accelerated the approval (238 vs. 376 days). With the same mean duration of 383 days the review times by the FDA are comparable to EMA review times.

Overall development times range between four and eighteen years. Comprehensibly, development times for diagnostic radiopharmaceuticals with a full dossier without reference to literature are much shorter compared to the development time of the diagnostic radiopharmaceuticals which base part of their dossier on published literature.

5. Evaluation of Theranostic Aspects of approved Radiopharmaceuticals

Within this Chapter the theranostic aspects approved by the regulators during the review of the previously described approved radiopharmaceuticals will be analysed. Based on the assessment reports from the EMA (EPAR) and the FDA, the theranostic approach in preclinical and clinical studies as well as the approval evaluation are discussed.

5.1. Theranostic Aspects in Preclinical Studies

As described in *Chapter 2 Theoretic Theranostic Approach*, some preclinical studies can be used both, for the diagnostic and the therapeutic part of the theranostic pair. As shown in Table *9*, all diagnostic radiopharmaceuticals fall under the microdose regime, and several diagnostic manufacturers of diagnostic radiopharmaceuticals used this facilitation.

Diagnostic radiopharmaceutical	Max mass dose [µg]	EMA/FDA review
[^{68}Ga]Ga-DOTATATE (NetSpot®)	50	*"Many nonclinical studies were performed using ^{177}Lu-DOTATATE or ^{175}Lu-DOTATATE. Since the only difference was the radiolabeled used, nonclinical data obtained using ^{177}Lu-DOTATATE or ^{175}Lu-DOTATATE is applicable for evaluating ^{68}Ga-DOTATATE"* (FDA)
		Not approved by EMA
[^{64}Cu]Cu-DOTATATE (DETECTNET®)	<100	*"From the review team perspective, there is enough clinical data in the studies conducted by the Applicant and the cited scientific literature to support the conclusion that a general toxicology study is not needed for this application"* (FDA)
		Not approved by EMA
[^{68}Ga]Ga-DOTATOC (U Iowa)	100	--- (FDA)
		Not approved by EMA
[^{68}Ga]Ga-DOTATOC (SomaKit TOC®)	40	Not approved by FDA
		"*Edotreotide biodistribution has been studied […] using both therapeutic and diagnostic radionuclides."* (EMA)
[^{68}Ga]Ga-PSMA-11 (UCSF/UCLA)	5	--- (FDA)
		Not approved by EMA
^{68}Ga-PSMA-11 (Locametz®)	25	*"[…] a bridging study to demonstrate comparability between the Applicant's kit and GOZ approved under NDA 212642 and NDA 212643."* (FDA)
		--- (EMA)
[^{68}Ga]Ga-PSMA-11 (Illuccix®)	25	*"[…] bridge between the Applicant's kit and Ga 68 gozetotide injection approved under NDA 212643 […]"* (FDA)
		Not approved by EMA
^{18}F-flotufolastat	100	--- (FDA)

(Posluma®)		Not approved by EMA
^{18}F-piflufolastat (PYLARIFY®)	4.4	--- (FDA)
		Not approved by EMA
^{18}F-piflufolastat (PYLCLARI®)		Not approved by FDA
		--- (EMA)

Table 9: Theranostic aspects in preclinical requirements in the approved diagnostic radiopharmaceuticals

In 50% (4/8) of the diagnostic radiopharmaceuticals in theranostic use, the FDA accepted limited preclinical data. These were mainly data from bridging studies or literature. Only in one case ([^{68}Ga]Ga-DOTATATE), a theranostic approach was acknowledged and preclinical data was used from the therapeutic radiopharmaceutical for the approval of the diagnostic radiopharmaceutical (NetSpot®). In one out of three diagnostic radiopharmaceuticals also the EMA follows the suggestion of the company to use biodistribution data from both Radiopharmaceuticals for the approval.

The therapeutic radiopharmaceuticals discussed in this thesis, Lutathera® and Pluvicto® use mass doses of 200 resp. max. 275 µg and do thus need the complete set of non-clinical studies described in the guidelines and summarized in Chapter 2.1 *Preclinical Requirements for Theranostic Radiopharmaceuticals.*

5.2. Theranostic Aspects in Clinical Trials

As described in Chapter 2, trial concepts for a parallel development of theranostic radiopharmaceuticals exist and are supported by the authorities, especially the FDA. Nevertheless, until today (June 2025) only one theranostic trial has been used for obtaining marketing authorisation of the diagnostic and the therapeutic compound in parallel. Only the VISION trial combined the clinical assessment of the diagnostic radiopharmaceutical Locametz® and the therapeutic radiopharmaceutical Pluvicto® for leveraging. Although the Phase III VISION trial is seen as the largest well-designed and executed trial of a theranostic pair [39], the impact of the theranostic design on sample size has not been described in the trial protocol and statistical analysis plan [40]. This is probably due to the fat that the exact exclusion rate was not known at the time of designing the VISION trial [41]. The leveraging approach is mainly

depicted in the imaging substudies which were introduced to assess the reproducibility of the diagnostic radiopharmaceutical.

Furthermore, concerns were risen, that no clinical data are available assessing whether radiopharmaceuticals alone are useful in predicting which patients are and are not likely to respond to therapy and also the VISION trial does not determine whether the PET/CT imaging criteria were useful in predicting the response to therapy [42]. Treatment benefit among patients with negative PET/CT results were not assessed. Thus, the FDA deemed a post-marketing study necessary to study the effects of therapy among patients who would have been excluded from VISION because of the imaging criteria.

5.3. Theranostic Aspects in MAA and NDA Evaluations

The use of theranostic synergies in the above-described approvals is still rather limited. Usually, the diagnostic compound is developed independently, often even by a different company (see Table *3*: Overview of clinical trials submitted for EMA approval of theranostic radiopharmaceuticals and Table *4*: Overview of clinical trials submitted for FDA approval of theranostic radiopharmaceuticals). Only Locametz® and Pluvicto®, both being developed by the same company and submitted and approved simultaneously both in the US and EU, although in two independent procedures, share some characteristics of a theranostic approach.

Theranostic aspect in approval pathways

<u>EU approval pathways</u>

In the EMA's approval documentation the European public assessment reports (EPARs), the term "theranostic" is never mentioned. Nevertheless, as mentioned above, Locametz® and Pluvicto® have been submitted for approval to the EMA in parallel and with a shared trial. This also is acknowledged in the EPAR of Pluvicto®, stating that

> "*the diagnostic tool used is under assessment in Europe too (parallel)*". Furthermore, the CHMP stated that "*within the context of the narrow indication (use of [^{68}Ga]Ga-PSMA-11 for patient selection of ^{177}Lu-PSMA-617 treatment) […]. No dedicated large clinical studies were requested considering the envisaged restricted use of gozetotide*."

Also in the assessment of SomaKit TOC®, some links to the therapeutic compound Lutathera® were made, e.g. in the Discussion on the benefit-risk assessment :

> "*The CHMP was not convinced that the efficacy data showed that ^{68}Ga edotreotide demonstrated a clinical benefit at predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET*"

or in the Discussion on clinical pharmacology:

> "*Data supporting efficacy of gallium (68Ga) edotreotide for predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited.*"

In the evaluation of Lutathera®, neither SomaKit TOC®, which was under evaluation by the EMA at the time of the submission of the MAA for Lutathera®, nor any other PET diagnostic radiopharmaceutical is mentioned. The preselection of patients took place using the SPECT tracer OctreoScan. Thus, although the company had a diagnostic radiopharmaceutical in development, it did not engage in the theranostic codevelopment, but relied on an existing diagnostic (SPECT) drug only.

US approval pathways

As outlined above, only Locametz®/Pluvicto® used theranostic synergies. Nevertheless, the the term "theranostic" was only mentioned by the FDA in the diagnostic radiopharmaceutical approval documentation:

> "*In summary, there are currently no imaging options to compete with Locametz® that have been approved for patient selection or any other **theranostic** radiopharmaceutical indication*", Source: Multi-disciplinary Review and Evaluation - Analysis of Current Treatment Options.

Consequently, the labeling of Locametz® is the only radiopharmaceutical with a reference to the therapeutic radiopharmaceutical (see Table *10*).

Theranostic aspects in labeling information

Approved indication of theranostic radiopharmaceuticals

In the EU, two therapeutic radiopharmaceuticals resp. Lutathera® and Pluvicto®. Have been approved so far. Neither the European label of Lutathera® nor of Pluvicto® indicate the method thus how to select suitable patients:

Lutathera® "*is indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults*." [43]

Pluvicto® *"[…] is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane-based chemotherapy*." [44]

The same applies the approved diagnostic radiopharmaceuticals which are part of a theranostic pair as they do not include references to their theranostic utility either.

Locametz® "*is indicated for […] Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated.*" [45]

SomaKit TOC® "*(gallium (68Ga) edotreotide) is indicated for positron emission tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastroenteropancreatic neuroendocrine tumours (GEP-NET) for localising primary tumours and their metastases."*[46]

At the timepoint of dossier submission for Lutathera® by Advanced Accelerator Applications, SomaKit TOC®, the diagnostic radiopharmaceutical of the same company was still under evaluation by the CHMP.

Regarding the FDA approvals, only the indication statement for the diagnostic radiopharmaceutical Locametz® includes information on the therapeutic counterpart Pluvicto® (see Table 10: Overview of indication statements of FDA approved radiopharmaceuticals).

	Approved indication (FDA)
GEP-NETs	
[^{68}Ga]Ga-DOTATATE (NetSpot®)	"*[…] localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients*"
[^{68}Ga]Ga-DOTATOC	
[^{64}Cu]Cu-DOTATATE (DETECTNET®)	*"[…] localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adults*"

[^{177}Lu]Lu-DOTATATE	*"[…] treatment of somatostatin receptor positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors in adults"*
PSMA positive prostate cancer	
[^{68}Ga]Ga-PSMA-11 **^{18}F-Piflufolastat (PYLARIFY®)**	*"[…] prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:* *• with suspected metastasis who are candidates for initial definitive therapy.* *• with suspected recurrence based on elevated serum PSA level."*
[^{68}Ga]Ga-PSMA-11 (Locametz®)	*"[…] prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer:* *• with suspected metastasis who are candidates for initial definitive therapy.* *• with suspected recurrence based on elevated serum PSA level.* *• for selection of patients with metastatic prostate cancer, for* ***whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated."***
[^{68}Ga]Ga-PSMA-11 (Illuccix®) **^{18}F-Flotufolastat (Posluma®)**	*"[…] prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum PSA level."*
[^{177}Lu]Lu-PSMA-617 (Pluvicto®)	*"[…] treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy"*

Table 10: Overview of indication statements of FDA approved radiopharmaceuticals

Theranostic aspects in the SmPC and Prescribing Information

Although not in the indication statement, the Summaries of product characteristics ("SmPCs") of the diagnostic theranostic radiopharmaceuticals include some statements on the respective therapeutic compounds. These statements are included in the sections *4.4 Special warnings and precautions for use* as well as *5.1 Pharmacodynamic properties* and reflect the limited data on the predictive value of the diagnostic compound as discussed above.

Drug	SmPC Section	Citation
SomaKit TOC®	4.4	"*Data supporting efficacy of gallium (68Ga) edotreotide for predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited (see section 5.1)*"
	5.1	"*Data available on clinical efficacy of gallium (68Ga) edotreotide for the indication of predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited.*"
Locametz®	4.4	"*Experience of use of gallium (68Ga) gozetotide PET for selection of patients for PSMA-based therapy is limited […] to selection of patients for treatment with lutetium (^{177}Lu) vipivotide tetraxetan*."

Pluvicto®	5.1	"*Patients underwent a gallium (68Ga) gozetotide […] (PET) scan to evaluate PSMA expression in lesions defined by central read criteria. Eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumour lesion with gallium (68Ga) gozetotide uptake greater than in normal liver*."

SmPC: Summary of Product Characteristics (EMA)

Table 11: Theranostic aspects in the Summary of Product Characteristics (SmPC)

In the US prescribing Information ("PI") on the respective theranostic counterpart are only found for the theranostic pair Locametz®/Pluvicto®. Especially in the Prescribing Information of the diagnostic radiopharmaceutical Locametz®, in alignment with the approved indication, information on the characteristics of the "*Imaging to Select Patients for Lutetium Lu 177 Vipivotide Tetraxetan Therapy*" is found in the Sections on *Image interpretation* (2.8), *Risk for Misinterpretation* (5.1) and *Clinical studies* (14).

Drug	**PI section**	**Citation**
Locametz®	2.8, 5.1 and 14	Section on "*Imaging to Select Patients for Lutetium Lu 177 Vipivotide Tetraxetan Therapy*"
Pluvicto®	14	"*Eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumor lesion with gallium Ga 68 gozetotide uptake greater than normal liver*."

PI: Prescribing Information

Table 12: Theranostic aspects in the prescribing information (US FDA)

Summarizing Chapter 5, the concept of using synergies for the development of theranostic pairs of radiopharmaceuticals is not yet well established in the assessment of theranostic radiopharmaceuticals by the regulators. While for the diagnostic radiopharmaceuticals associated with Lutathera® (SomaKit TOC® and NetSpot®), synergies are described in the preclinical part of the assessment report, the theranostic synergies of the pair Locametz®/Pluvicto® are focused on the clinical part and the approval pathway. Consequently, also the labeling information and SmPC resp. PI of all radiopharmaceuticals beside Locametz®/Pluvicto® do not include any information on their theranostic use.

In this regard, SomaKit TOC® (EU) forms a special case since its approval was based on well-established use, thus no dedicated trials were carried out. Thus, even a warning against its

use as part of a theranostic pair ("*for predicting and monitoring of therapeutic response*") was included in the SmPc.

6. Regulatory Considerations for Theranostics

A decade ago, Heertum et al. [2] noticed that the process of achieving regulatory approval for new diagnostic imaging drugs is extremely challenging, which he highlighted by the fact that only a handful of new radiotracers have received FDA approval in the previous decade. He emphasized that radiotracers, although typically administered at doses magnitudes lower than therapeutics and designed to measure molecular processes rather than modifying them, are regulated as if they carried the equivalent risk of a therapeutic radiopharmaceutical [2]. Within this Chapter approaches to facilitate and promote the approval of theranostic radiopharmaceuticals will be discussed.

6.1. Market Environment

Public and political support of theranostic radiopharmaceuticals

Many governments around the globe have included cancer treatment as a national healthcare priority. Beside numerous training initiatives [47,48], policy initiatives like the Stakeholder Political Alliance For Radioligand Cancer Therapies (SPARC) [49] bring together policymakers, experts in the field of nuclear medicines and oncology and patient representatives to raise awareness for the specific characteristics of radiopharmaceutical therapeutics.

Pharmaceutical companies developing theranostic products actively lobby for policy changes including reimbursement policies or decreased regulatory and development hurdles. In the EU, e.g. the Nuclear Medicine Europe Association (NMEU) with their Regulatory Affairs Working Group fosters the communication with regulatory authorities with symposia, publications and position papers to address the challenges of theranostics the industry is facing [50].

Additionally, specialist societies like the SNMMI (Society for Nuclear Medicine and Molecular Imaging) provide support for approval and reimbursement processes. Especially SNMMI`s FDA Task Force works to create a more efficient and timely process for approvals of new tracers, i.e. Axumin® and NetSpot® in 2016 [51].

Also the European Association of Nuclear Medicine (EANM) is promoting the theranostic idea. Besides education, they also facilitate several projects on theranostics. Two examples are the Thera4Care [52] Project which does not include regulatory approaches beside trial framework and the Tender SIMPLERAD [53] project which works on the implementation of relevant

European legal requirements for therapeutic nuclear medicine. Thera4Care brings together partners from 14 European countries and the United States under the Horizon Europe framework, and part of the Innovative Health Initiative (IHI), a public-private partnership ("PPP") between the EU and the European life science industries (see Chapter 6.1 Subchapter *Public-Private Partnerships*) [54].

The Lutathera® case

On July 20th, 2017, the CHMP issued a positive opinion for granting a marketing authorisation to Lutathera® (submission of application April 26th, 2016) in the EU. Although in the US, the NDA rolling submission of data was completed at the same time (April 28th, 2016), the FDA issued a complete response letter on December 19th, 2016 as data submitted in this NDA was found to be materially incomplete, inaccurate, untraceable, and inconsistent. The *Complete Response Letter*, which followed a discipline review letter issued in November 2016, requested new subgroup data, a safety update, and that revisions be made to the previously submitted data. The letter did not request the initiation of additional studies of Lutathera®. Thus, Lutathera® was already available in Europe, but not in the US. As a reaction hereto, many patients turned to online communities, social media, and advocacy groups. Patient advocacy organizations, such as the Neuroendocrine Tumor Research Foundation (NETRF) and the Carcinoid Cancer Foundation, actively campaigned for the approval of Lutathera® [55]. Subsequently, the FDA approved Lutathera® after complete response resubmission, which was submitted to the FDA a few days after the approval of Lutathera® in the EU, within 6 months for the use in the US. The impact on the above describe initiatives are hard to quantify, but with high likelihood they played a role in creating a supportive environment by raising the awareness and highlighting the benefit of the treatment.

Public-Private Partnerships

The principal idea of a public-private partnership ("PPP") is that for-profit institutions from the private sector (e.g. pharmaceutical industry) meet with institutions from the public sector (e.g. academia, international organisations, governments) to share their knowledge, expertise, resources and investment to cooperate in complex challenges, which may not be accomplished by a single institution. An example for the PPP is the innovative health initiative between the EU and the European life science industries, who fund projects to support the development and proof of principle of new clinical applications of theranostic solutions [56].

Intellectual Property

In 2009, Agdeppa et al. stated that the therapeutic drug and imaging agent industries rely on exclusivity of intellectual Property (IP) to gain an advantage over competitors; however, the lower return on investment for imaging drugs causes the imaging industry to be very selective of in-licensed IP [57]. Although, markets for new targeted tracers appear to be limited to niche indications, making it difficult for imaging companies to justify the costs associated with in-licensing and developing new tracers, especially for those that are not yet far enough along in the development process [57]. As a solution to challenges with tracer IP, the authors mentioned PPP to secure tracer IP ownership of potentially small-market indications. They suggest academics, industry, and societies like SNMMI to partner for patent pooling of drugs with small indications.

Although Adeppa et al. stated in 2009 that some academic centres become as protective of their technology as institutions and adopt the same IP protection as for-profit companies [57]; he was proofed wrong by two examples: Both the development of [^{68}Ga]Ga-PSMA by UCSF/UCLA and of[^{68}Ga]Ga-DOTATOC by the University of Iowa, are without patent protection (see Sections on *Patent situation and market exclusivity* in Annex 3), proofed him wrong. As academic institutions waived exclusivity and opened the market to both academia and industry to submit abbreviated NDAs to facilitate access of these drugs to patients. Consequently, PSMA-11 was widely used and became the de facto global standard for PSMA-PET in an incredibly short time. As it is distributed by numerous manufacturers worldwide and is available as a labeling kit, it is still one of the most commonly used PSMA tracers, even if there are other imaging drugs likely to be more effective [29].

New EU pharmaceutical legislation

As described in Annex 1 and Annex 2, the requirements and procedures for marketing authorisation, are primarily laid down in Directive 2001/83/EC and in Regulation (EC) No 726/2004. On April 26th 2023, the Commission adopted a proposal for a new Directive and a new Regulation to revise and replace the existing general pharmaceutical legislation [58]. In the proposal for the new directive [59], the well-established use route of obtaining a marketing authorisation is regulated via Article 13 "Applications based on bibliographic data". New specific conditions, like the exclusion of medicinal products where the reference medicinal product is or has been authorised for the active substance of the medicinal product concerned, shall be applied. These conditions will only restrict the use of the well-established use pathway for generics or non-prescription medicinal products, the use for radiopharmaceuticals will likely not be impacted.

While currently all therapeutic radiopharmaceuticals are approved using fixed standard treatment doses, and patient individual dosimetry is not mandatory for in-label use [60], recent regulatory developments [61] aim towards a mandatory dosimetry scan. These dosimetry scans shall provide careful treatment with a targeted dose for every single patient. For ^{177}Lu-coupled radiopharmaceuticals no surrogate radionuclide is required as ^{177}Lu emits a β-particle emission, which is used to kill cancer cells, but also gives off a γ-photon emission and thus can be used for imaging [62]. As all currently approved therapeutic radiopharmaceuticals use ^{177}Lu, no major regulatory hurdle is foreseen. Nevertheless, probably variation applications for an additional strength (EMA) and a new indication (dosimetry) need to be submitted by the MAH.

In the context of the new pharmaceutical legislation, EANM proposes further adjustments regarding the nuclear medicine field [58] which are out of scope of this thesis.

6.2. Cost Effectiveness and Efficiency

As discussed previously, development of radiopharmaceuticals is very expensive [23,63]. Trial costs of up to 50 Mio. $ (Phase 3 VISION Trial, information from GlobalData) are a major part of the total development costs of radiopharmaceuticals. In case of the above discussed theranostic approach, if not already available, even two radiopharmaceuticals (the diagnostic and the therapeutic radiopharmaceutical) need to be developed. As the profit is much higher

for a therapeutic radiopharmaceutical, several developers of new therapeutic Radiopharmaceuticals build on an already approved diagnostic radiopharmaceutical (see Chapter 3.2. *Ongoing Clinical Trials for Theranostic Radiopharmaceuticals* and Annex 5 for a detailed list) to be cost efficient (Focus on developing a theranostic pair at the lowest cost). Nevertheless, several theranostics pairs are still developed in parallel. The cost-effectiveness (best profit for the price paid) of this approach is given by a number of synergies in the development process:

Omitting one/two diagnostic Phase 3 trials

Although diagnostic development costs are reported to be lower compared to therapeutic radiopharmaceuticals ($100 - $200 Mio vs. $800 - $1.700 Mio) [63], sales numbers as well as reimbursement is much lower for diagnostic radiopharmaceuticals. Thus, a combination of the development of the diagnostic and the therapeutic compound in a combined trial significantly reduce the cost of drug development.

Lower sample size for confirmatory trial

As discussed in Wang et al. 2022 [26], sample sizes for confirmatory therapeutic trials can be lowered by introducing a predictive diagnostic radiopharmaceutical. If the costs of screening all patients for the positive biomarker are lower than the studying additional patients (if no preselection takes place) a theranostic design is cost-effective. As the price for a therapeutic radiopharmaceutical is significantly higher than for a diagnostic compound, this is probably most often the case. An exemplary calculation for PSMA-targeted radiopharmaceuticals assuming 90% prevalence of PSMA expression [26] would lead to approx. 20% sample size saving (see Figure *2*). With an assumed cost of 7.000€ [64] – 50.000€ [65,66] (depending on region and reimbursement) for the therapeutic Pluvicto® dose (6 doses as per clinical trial protocol, upper limit for commercial dose) and 1.100€ [65] – 5.000€ [67] for the diagnostic Locametz® and patient numbers in a trial of 500. Using preselection via the predictive diagnostic radiopharmaceutical could save costs of three to four million € using conservative calculations.

Synergies in the preclinical and clinical development process

Also using synergies as described in Chapter 5.1 *Theranostic Aspects in Preclinical Studies* and Chapter 2.2 *Theoretic Clinical Trial Designs,* help to make the development of theranostic pairs cost-efficient. Non-clinical data assessed for the therapeutic compound can be used for the diagnostic compound as well, avoiding the necessity of dedicated toxicology studies for the

diagnostic compound. Furthermore, using a leveraging concept, comprehensive data on the diagnostic compound can be obtained in the pivotal therapeutic trial. By including imaging substudies and not only focusing on the predictive value of the diagnostic compound, pivotal data for an independent approval of the diagnostic compound can be assessed without the need of a dedicated diagnostic Phase 3 trial.

In addition to the above-described concepts, the regulatory frameworks discussed in the next chapter feature linkages between diagnosis and therapy and, hopefully, cost-effectiveness of development of theranostic radiopharmaceuticals can be increased and further theranostic pairs will come to market.

6.3. Regulatory Frameworks that Feature Linkages between Diagnosis and Therapy

Application and Modification of existing regulatory pathways

FDA and EMA already have several tools at hand to expedite development and approval of drugs. As shown in Table 16 and Table 18 (see Annex 4), especially for the RPs approved by the FDA, this possibility has been used extensively. To further streamline the development of real theranostic pairs, an automatic fast-track procedure for companion diagnostics to breakthrough therapy therapeutic radiopharmaceuticals likely could accelerate the approval of theranostics in the US. Furthermore, an accelerated approval of both, the diagnostic and the therapeutic RP if they have been solely used in combination and clinical benefit can be predicted but not measured could further strengthen the theranostic idea.

In regard to the EU, the parallel conditional marketing authorisation of diagnostic and therapeutic RP could address the low risk profile of radiopharmaceuticals and can meet the unmet medical needs of patients. This approach would further support the practice already in place to approve diagnostic radiopharmaceuticals based on published data and well-established use.

Companion diagnostic

Although from a regulatory perspective (see section 1.5 and Annex 2) not foreseen, the term “Companion Diagnostic” is often associated with theranostic radiopharmaceuticals [7,8]. Sometimes as an intermediate stage on the way to theranostics [68], sometimes as a synonymous term [7,8].

For example, Lee et al. strengthen the concept of in-vivo CDx by stating that

> "*nuclear imaging is used for the similar purpose of the prediction of desired biodistribution and thus the expected effect on the target tissues/organs by administering the "radiolabeled" novel therapeutic products*" [8].

Beside numerous publications discussing about CDx radiopharmaceuticals, also the FDA uses the term in three FDA's Multi-disciplinary Review and Evaluations (see Table *13*). Nevertheless section 4.4 *Devices and Companion Diagnostic Issues* in the Multi-disciplinary Review and Evaluations documents was defined as not applicable for most of the radiopharmaceuticals discussed in this thesis. Only in the documentation for Locametz® and Pluvicto® entries can be found. Of note, the companion diagnostic-related wording in the documentation for Pluvicto® (see Table *13*) indicates that there has been a Premarket approval application ("PMA") for [^{68}Ga]Ga-PSMA-11. As introduced in Section Companion diagnostics FDA, PMA applications are the regulatory pathway for Class III medical devices. Beside this mention, no further information can be found in the public resources. A search in the FDA premarket approval database [69] gave no result. As the NDA for Locametz® was submitted two days after the Pluvicto® NDA, it is unlikely, that a PMA application was submitted at the same time as stated in the FDA assessment. Thus, it is likely an unclear wording and not referring to a medical device/companion diagnostic procedure which was run in parallel. This assumption is supported by the fact that the NDA number was mentioned together with the PMA, but no PMA number was reported.

Drug	Reference	Quote
Lutathera®	FDA Memorandum of meeting minutes (Type C meeting)	*"AAA may reference data in the NDA for gallium DOTA Octreotate, the companion diagnostic product, if the NDA for this test is approved prior to the approval of ^{177}Lu-DOTA0-Tyr3-Octreotate"*
Pluvicto®	Summary review Section 4.4. Devices and Companion Diagnostic Issues	No verbatim reference to companion diagnostic *"Premarket approval application NDA 215841 for ^{68}Ga PSMA-11 for use with PET-CT to select patients for treatment with 177-Lu vipivotide tetraxetan was submitted to CDER for the following indication: […]"*
	FDA assessment of Review of 8.1 Relevant Individual Trials Used to Support Efficacy	*"Premarket approval application NDA 215841 for ^{68}Ga PSMA-11 for evaluation as a companion diagnostic along with this NDA submission was submitted to CDER for the following new indication […]."*
	Memorandum of meeting minutes (EOP2 Meeting)	*"We recommend that you clarify whether ^{68}Ga-PSMA-11 is being developed strictly as a companion diagnostic for use with ^{177}Lu-PSMA-617 or as a "stand-alone" diagnostic imaging drug."*

Locametz®	4.4. Devices and Companion Diagnostic Issues	No verbatim reference; Reference to FDA's Multi-disciplinary Review and Evaluation for Pluvicto®

AAA: Advanced Accelerator Applications; EOP2: End of Phase 2

Table 13: Use of the term "Companion Diagnostic" in connection with theranostic radiopharmaceuticals

None of the European EPARS used the term "Companion Diagnostic" for the diagnostic part of the theranostic pair.

In summary, although in the last decade, more theranostic radiopharmaceuticals came to the market, the pathway for the "companion diagnostic" radiopharmaceutical is still not facilitated and still shares many of the same challenges as therapeutic drug development described in Heertum et al. 2015 [2]. In the next section possible measures to facilitate the development and approval of theranostic radiopharmaceuticals based on the CDx concept are discussed.

Translating the companion diagnostic concept to theranostic radiopharmaceuticals

As discussed above, the diagnostic part of a radiopharmaceutical theranostic pair shares many similarities with CDx. Especially in the US where the CDx definition even includes imaging tools, the only difference is the clear wording, that only medical devices can be a CDx. As diagnostic radiopharmaceuticals have a pharmacological mode of action although if administered in a microdose being not pharmacologically active, they cannot be declared as medical devices.

In the EU the incompatibility of radiopharmaceuticals with being a CDx is clearly stated in the MDCG 2022-5: "Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices", explaining that

> "*As per the definition of a medicinal product in Article 1 (2)(b) MPD, the mode of action for the diagnostic substance(s) used in or administered to human beings is not a criterion for deciding the regulatory route, hence substances such as X-ray contrast media, NMR enhancing agents, SPECT- and PET-radiopharmaceuticals, fluorescein strips for diagnostic purposes, radioactive tracers, and substances for tumour identification are medicinal products*."

While the European IVDR, replacing the old In Vitro Diagnostic Medical Device Directive (IVDD), increased requirements for the approval of CDx, the recent trend in US are moving towards facilitating the approval of CDx. It is therefore not desirable to translate the

requirements. Especially the provision that the notified body is required to consult a competent authority, laid down in the IVDR to diagnostic radiopharmaceuticals would add further complexity to the approval process. In contrast to this, the recent announcement by the FDA to reclassify already approved CDx as Class 2 medical device allows new CDx to refer to these predicate devices. This step was taken to increase competition and access to these important tests [10]. Thus, innovative CDx still underly the risk-based approach. Diagnostic radiopharmaceuticals, although often not pharmacologically active are drugs that, in contrast to in-vitro devices bare the risk of side effects. As thus in the opinion of the author of this thesis it is not justified to treat them similar to Class 2 medical devices. Taking this into account and consequently considering the requirements for Class 3 medical devices reduces the benefits of handling radiopharmaceutical CDx according to the legal basis of medical devices markedly. The PMA being a rigorous process involving the demonstration of the device´s safety and efficacy does not differ much from the NDA process. With its less regulated nature it may facilitate approval but looking at the timeline discussed above, with a mean duration from submission till approval of 369 days for the above discussed diagnostic radiopharmaceuticals and 399 days for PMA devices, the more regulated NDA process seems to be beneficial for a faster approval.

Also a PhD thesis from 2019, discussed the topic “Radiopharmaceuticals being used as Companion Diagnostics?” based on statements of the interviewees from nuclear medicine physicists. The nuclear medicine physicist interviewed for this thesis would like to get more radiopharmaceuticals approved via the concept of CDx, but similar to the above remarks, the author does not see the chance of success as great [70]. While the above discussion mainly focusses on the difficulties laying in the regulatory framework, the interviews suggest that even for the radiopharmaceutical industry the development of an imaging CDx is currently not attractive as the market for a CDx is too limited. The commercial risk is higher compared to classic diagnostic products since there is a chance that either the therapeutic will fail or a new development will replace the therapeutic drug or that the test will not be reimbursed [70]. The direct link to the therapeutic drug limits the use of the test, and currently, these CDx are poorly reimbursed [70].

In summary, regulatory requirements for approvals of in-vitro CDx have no advantage over the current regulatory framework for diagnostic radiopharmaceuticals. As such there is no need to strive for a change in regulatory framework in this direction.

Co-development

The EMA uses the term “Co-development” in the context of biomarker-based assays [71,72] and discusses three scenarios all assuming higher anti-tumor activity if two drugs are combined and thus not applicable to the theranostic approach. Co-development in regard to CDx is recommended in “Frequently asked questions on medicinal products development and assessment involving companion diagnostic (CDx)”, but not further specified. Although several aspects of clinical trial design are discussed in the respective guideline[72] no regulatory considerations are included.

In the US legislation, Co-development is according to the *Guidance for Industry on Codevelopment of Two or More New Investigational Drugs for Use in Combination,*

> “*the development of two or more new drugs that have not been previously developed for any indication to be used in combination to treat a disease or condition*” [73].

Furthermore, in 2016, the FDA has published a draft guideline “Principles for codevelopment of an in vitro companion diagnostic device with a therapeutic product” [74] which mandates the development of in vitro diagnostic CDx devices contemporaneously with the approval of the novel therapeutic products. In 2022 Wang et al. [26], affiliated with the FDA, explicitly mentioned co-development as a regulatory framework that feature more direct linkages between diagnostic and therapy.

Unfortunately, both guidelines are not applicable to theranostic radiopharmaceuticals. Regarding the *Guidance for Industry on Codevelopment of Two or More New Investigational Drugs for Use in Combination* [73] the FDA restricts the application of the codevelopment approach to new investigational drugs cannot be developed independently. As the therapeutic and the diagnostic part of the theranostic radiopharmaceutical can be developed independently without any risk for the patient or limits in efficacy, the use of codevelopment per default based on this guideline is not possible. The other guideline cited above refers to in-vitro CDx and is as thus also not applicable to in-vivo CDx as diagnostic radiopharmaceuticals are.

The term “Co-development” is sometimes also used for the shared development of two or more parties, e.g. academic institutions or other non-for-profit research institutions [70],

which shall be in this thesis be discussed under public-private partnerships (see Chapter 6.1 Subchapter *Public-Private Partnerships*).

In the next section possible measures to facilitate the development and approval of theranostic radiopharmaceuticals based on the co-development concept are discussed.

Translating the co-development concept to theranostic radiopharmaceuticals

Although the above mentioned guidances are currently not applicable for theranostic radiopharmaceuticals, some of the features might facilitate approval of theranostic pairs of radiopharmaceuticals. One IND for the combination that covers all of the drugs in the combination at the point in time at which the sponsor initiates clinical trials of the combination (if not intended for use as a stand-alone diagnostic resp. therapeutic radiopharmaceutical) could enable a closer linkage between the diagnostic and the therapeutic radiopharmaceutical. Considering that complete information needs to be included regardless of whether one or two INDs are filed, and no extra costs arise from a 2nd IND, putting all information into one IND might increase complexity and be at the expense of clarity and conciseness. In Europe one central application via CTIS per trial makes the necessity of a combined application obsolete.

Using the same marketing application the combination and monotherapy uses could decrease the costs for the MAH markedly. With current costs of more than $4Mio [75] (FDA) respectively up to 865.000€ [76] (EMA), the restriction to one fee for the diagnostic and therapeutic radiopharmaceutical would foster the development of theranostic pairs.

The “Principles for codevelopment of an in vitro companion diagnostic device with a therapeutic product” [74] address some important points which should also be considered for the co-development of the diagnostic and therapeutic part of a theranostic radiopharmaceutical pair. The most relevant point is the coordination of review times resp. contemporaneous Marketing Authorisation. As discussed above, the contemporaneous marketing authorisations for the therapeutic product and CDx is of high importance. Although EMA and FDA managed in past that applications for theranostic pairs which were handed in simultaneously (Locametz® and Pluvicto®) have been assessed and approved in the same timeline, care should be taken to ensure that this is also the case for future applications. To enable parallel approval of the theranostic pairs, the guideline proposes several measures some of which should also be considered for theranostic radiopharmaceuticals. The described “modular” PMA process, which is comparable to rolling review in allowing the applicant to submit discrete sections, or

modules, of the application as they are completed, allows to resolve deficiencies identified by the reviewers earlier in the review process, making the final review more likely to be completed concurrently with review of the therapeutic product. Also the concepts of priority review and accelerated approval as discussed in the Chapter 6.3 Subchapter *Application and Modification of existing regulatory pathways* are mentioned in the guideline [74].

Real-world data

To ensure safety and efficacy, robust data from multicentre trials are required for marketing approval of new drugs, including radiopharmaceuticals. These trials are generally conducted under very specific conditions (carefully selected patient populations, specific inclusion and exclusion criteria incl. limited concomitant medication and exact timing of procedures). Consequently, data from such trials often not accurately reflect the results and outcomes in the real-world environment when drugs are administered to patients with additional medications, not clearly defined disease burdens, other ages and ethnicities. Thus it is discussed whether the inclusion of real world evidence might help to better understand how well data from clinical trials can be reproduced in the real world [77]. The FDA encourages sponsors to use real-world data for post-authorisation studies [78]. Nevertheless, for generating the pivotal evidence for approval, real-world data still suffers from requiring long time till it is available as well as low standardisation making its assessment difficult.

The FDA approved Lutathera®, based in part on data generated through the expanded access program. Lutathera®'s approval was supported by two trials. One was a randomized controlled trial with 229 patients. The second trial was based on data from a single-arm, open-label trial of 1.214 patients with somatostatin receptor-positive tumors, including GEP-NETS, who received Lutathera® at a single site in the Netherlands [79]. The expanded access protocol data enabled a broader indication than the trial submitted in the NDA [80]. Further examples of use of real-world data for approval of radiopharmaceuticals are the approvals based on literature resp. well-established use. A large number of diagnostic radiopharmaceuticals (see Table *7*) have been approved by the FDA based solely, or in large part, on the clinical trial experience described in published reports, including reports of exploratory trials performed at a single clinical site [81]. Also the European approval of SomaKit TOC® was based on well-established use using the available published reports from academia. This approach acknowledges the

high development costs and regulations of diagnostic radiopharmaceuticals which are out of proportion compared to the low risk profile and the limited reimbursement.

7. Concluding Discussion of the Ideal Trial Design and Approval Pathway for Theranostic Radiopharmaceuticals

In this Chapter, based on the discussions and explanations given in the other Chapters, a conclusion on the optimal development concept and approval pathway will be drawn.

Reviewing the past approvals of the last 10 years, it seems like the requirements by the FDA for approving diagnostic radiopharmaceuticals in theranostic use rose. While NETSPOT® ([^{68}Ga]Ga-DOTATATE) in 2016 was approved solely based on literature in a 505(b)(2) procedure, a few years later [^{68}Ga]Ga -PSMA-11, [^{68}Ga]Ga-DOTATOC and [^{64}Cu]Cu-DOTATATE received their approval in 2019/2020 based on one pivotal trial or single centre experience. Further new diagnostic radiopharmaceuticals like ^{18}F-piflufolastat in 2021 and ^{18}F-flotufolastat in 2023 were approved on the basis of two pivotal Phase 3 trials in a 505(b)(1) procedure. Just recently, Pixclara (F-18 FET), the related diagnostic to the therapeutic ^{131}I-TLX101 (not approved) was rejected by the FDA in April 2025 due to missing confirmatory clinical evidence. Pixclara NDA was submitted based for a 505(b)(2) procedure using Phase 2 data in 2024 [82]. Pixclara is recommended in the international oncology guidelines for glioma imaging and received priority review, orphan drug designation ("ODD") and Fast track designation.

A comparable trend may also be anticipated in Europe. So far, the approval of well-established use for SomaKit TOC® in 2016 remained the only approval not using the standard pathway (Article 8(3), Directive 2001/83/EC).

Interestingly, for diagnostic radiopharmaceuticals, developed in a theranostic set-up (Locametz®/Pluvicto®), the EMA agreed on less clinical evidence ("*within the context of the narrow indication (use of [^{68}Ga]Ga-PSMA-11 for patient selection of ^{177}Lu-PSMA-617 treatment) […]. No dedicated large clinical studies were requested considering the envisaged restricted use of gozetotide.*").

While other diagnostic methods like MRI or CT are accepted to give results which need careful interpretation by the medical specialist, the demand of both EMA and FDA regarding diagnostic radiopharmaceuticals is to give unambiguous results and proof of their impact on patient management before approval. Trial designs to show an impact on patient management require high patient numbers, thus are costly and time-consuming. Interestingly this is also mirrored in the current landscape of theranostics under development. None of the nine therapeutic

radiopharmaceuticals under development (selection based on The Current Status of Global Theranostics in 2024 (Source: Oppenheimer & Co. Research), see also Figure 3), are connected to a new diagnostic radiopharmaceutical under development; eight out of nine are using an approved diagnostic radiopharmaceutical.

7.1. The Ideal Theranostic Trial Concept

Among those new therapeutic radiopharmaceuticals which are not linked to an existing diagnostic radiopharmaceutical, most are investigated in theranostic trials (see Table *19*), thus developing the diagnostic radiopharmaceutical in parallel to the therapeutic radiopharmaceutical. In the light of the described increasing need of evidence for stand-alone diagnostics, this concept seems to be the most promising way for companies wanting to develop a new theranostic pair. This assumption is supported by the recent publication from the FDA imaging division fostering theranostic trial design and the EMA's assessment report for Pluvicto® indicating that less clinical evidence is needed for the restricted use of diagnostic radiopharmaceuticals in the theranostic setting. Also from a financial point of view, the co-development in a theranostic trial is advisable. Compared to pure therapeutic trials, theranostic trials are only insignificantly more expensive. Extra costs such as for additional imaging scans are neglectable compared to the costs of opening study sites, the basic fee for the CRO conducting the trial and personnel costs at the company. Furthermore, if the approval does not comprise the use as a stand-alone diagnostic, the loss of sales often does not outweigh the higher development costs of diagnostic Phase 3 trials since reimbursement for diagnostic radiopharmaceuticals is much lower compared to therapeutic radiopharmaceuticals (see Chapter 6.1).

An argument against the theranostic trial concept may be, that the diagnostic compound might be developed faster, thus might be approved earlier as there are less safety concerns. Taking into account that many trials follow the microdosing approach, often no dose finding studies are needed and the diagnostic radiopharmaceuticals under development can start directly with a Phase 2 or 3 trial (Example: PentixaFor [83]) based on published evidence from investigator-initiated studies. Furthermore, when tying the diagnostic and the therapeutic compound together, the risk of failure for this theranostic pair is higher as both radiopharmaceuticals fail if one fails. Nevertheless, as previously discussed, the regulatory requirements appear to have increased, thus a thorough trial concept is needed if one aims on an approval based on one

pivotal trial only. Given this development, the stand-alone development of a diagnostic radiopharmaceutical seems less attractive than a theranostic concept with leveraging.

In summary, a theranostic trial concept using leveraging respectively including endpoints for assessment of the diagnostic radiopharmaceutical might be complex, however, the advantages overweight by far. Promoted by the FDA imaging division, this approach leads to a parallel development of the diagnostic and therapeutic radiopharmaceutical allowing a coordinated overall strategy in a cost-effective way.

7.2. The Ideal Theranostic Approval Pathway

While the theranostic trials are still in the early stages, the approval process, both in the US and the EU, already seems to be prepared for theranostic approvals. In the assessment of the trailblazer Locametz®/Pluvicto®, several aspects towards a framework for theranostic radiopharmaceuticals have been employed. Both agencies reviewed the two applications in parallel within the same timelines, which not prolonged compared to other approvals. Still, the theranostic features in the regulatory assessment described for Locametz®/Pluvicto®, are not laid down in any legal framework. A clear “Theranostic development of radiopharmaceuticals” guideline similar to the guidelines for co-development or the development of CDx would provide reliability enabling better planning, thus fostering the development of theranostic radiopharmaceuticals.

Further regulatory frameworks featuring the linkage between therapeutic and diagnostic regulatory pathways have been discussed in Chapter 6.3. The co-development framework employs some important concepts to enable a streamlined development of the diagnostic and the therapeutic drug, but most of these concepts already exist and could also be used without terming it co-development. These existing approaches like reduction of fees, linking designations between the diagnostic and therapeutic products and aligning assessment timelines could further promote the development of theranostic radiopharmaceuticals. These supportive measures should be included in the above-mentioned guideline as well. Also, the needed evidence should be addresses in the “Theranostic development of radiopharmaceuticals” guideline. Further, a common understanding which evidence needs to be shown when seeking

approval, also taking into account the special nature of diagnostics in general and the theranostic concept would provide clarity for trial design and conduct.

Such a guideline by the regulatory agencies would support those developers currently performing early theranostic clinical trials to smoothly transfer such to parallel theranostic approvals of the diagnostic and therapeutic radiopharmaceutical. This would also reduce the complexity of the theranostic development, thus increase the speed and decrease the costs of bringing theranostic radiopharmaceuticals to the market.

7.3. The Ideal Environment for Theranostic Developments

Besides choosing the ideal clinical trial concept and optimizing the approval pathway, the impact of the general environment was also discussed in Chapter 6.1. The whole market environment plays a pivotal role in bringing a drug to the market. Factors like the patent status and public and political support have a huge impact on the development and approval of new drugs. radiopharmaceuticals without a patent protection can be brought to market much faster and at lower costs as seen for PSMA-11 [29]. Also, support from the public and politics for specific radiopharmaceuticals have accelerated up the approval processes in the past. Unfortunately, these factors can rarely by controlled by the developing company.

In his PhD thesis, Konwalinka discussed [70] the optimal environment for the development of diagnostic radiopharmaceuticals. He stated that the traditional development process is suitable for the approval of new diagnostic radiopharmaceuticals, but what may be needed further, is a closer co-operation and coordination within academic institutions, as well as a coordinated approach with small and medium-sized enterprises (“SMEs”). From his point of view, SMEs are best suited to drive the development of new diagnostic radiopharmaceuticals since they have a good understanding of pathology and human biology, close collaborations with academic institutions, a flexible and rapid decision-making process and they are willing to take risks.

This approach of PPPs discussed in Chapter 6.1, is already used frequently in the development of radiopharmaceuticals. Examples are PSMA-11, purely developed by academia and released to be marketed by industry and amended by an industry trial for theranostic use (Pluvicto®). Also, the trend of radiopharmaceutical development in SMEs and later take-over by large pharma companies could be clearly observed during the last years. In 2024 Novartis bought

Mariana Oncology, Eli Lilly took over Point Biopharma. AstraZeneca acquired Fusion Pharmaceuticals and Bristol Myers Squibb secured RayzeBio with its lead Phase 3 compound RYZ101. This ecosystem of big companies, with investment mechanisms, but not willing to take the risk of early development and small innovative companies breaking at translational requirements is well recognized and endorsed within the community [84].

Another approach, suggested 20 years ago, was the partnering of instrument and drug companies [85]. Although some instrument companies extended their business to production solutions (Cyclotrons, radiochemistry systems and tracer production facilities) [86], none of the instrument companies partnered with drug companies so far, thus this anticipated way of fostering development of new diagnostic radiopharmaceuticals could not be observed so far.

In summary an optimal environment for developing theranostic radiopharmaceuticals is an ambience with supportive regulators, public and politics. Partnering is the key for driving radiopharmaceutical development. Early communication between all stakeholders and strategic partnerships between small and big companies as well as with academia seems most promising to bring these lifesaving theranostic radiopharmaceuticals to the market.

8. Summary and Outlook

This thesis discussed the clinical trials and approval pathways for theranostic radiopharmaceuticals in the US and the EU. The current use and further potential of synergies in the development of diagnostic and therapeutic radiopharmaceuticals in theranostic settings have been described.

Especially the concept of radiopharmaceutical CDx was highlighted as regulators and researchers mention the concept frequently in the context of facilitating theranostic approvals. Although several publications emphasize a benefit in treating diagnostic radiopharmaceuticals as companion devices, in this thesis, which takes into consideration the updated regulatory framework, especially in the EU, the advantages of such changes could not identified. The traditional regulatory framework of drugs is appropriate for radiopharmaceuticals.

Reviewing the currently approved radiopharmaceuticals, one pair of theranostic radiopharmaceuticals has employed several aspects towards a framework for theranostic radiopharmaceuticals already, e.g. FDA and EMA reviewed the application in parallel within the same timelines, which not prolonged compared to other approvals. While most approvals in the last decade did not use the clinical synergies of a theranostic study design, in this case also the clinical studies were shared, a strategy which can also be observed for the current theranostic radiopharmaceuticals under development.

As most approved theranostic radiopharmaceuticals did not employ synergies, measures to facilitate the development and approval of theranostic radiopharmaceuticals would foster the growth of this field. Assuming a parallel development of the theranostic radiopharmaceutical pair by the pharmaceutical companies, the approval pathway needs be harmonized also.

Facilitations which might support developers of theranostic radiopharmaceuticals are, among others, contemporaneous marketing authorisations for the therapeutic and the diagnostic product, automatic extension of designations to the diagnostic product and fee reductions.

As shown in Chapter 7.2 *The Ideal Theranostic Approval Pathway,* beside a change in companies strategies towards more theranostic development also clarity in the regulatory environment is needed. While, the EMA has recently drafted a concept paper for a guideline on the Clinical evaluation of therapeutic radiopharmaceuticals, the guideline on clinical evaluation of diagnostic agents is already more than 15 years old. The current concept of theranostics is

neither incorporated nor planned to be included in either one of them. Thus, a guideline on theranostic radiopharmaceutical development will hopefully be tackled by both agencies soon.

Looking into the future of the clinical development, this thesis shows that the VISION trial referred to as the developmental paradigm for theranostics [39] cannot be the end of theranostic trial design. Current publications describe approaches for predictive and prognostic radiopharmaceuticals and their use for improving therapeutic trial design as well as the combined development of a theranostic pair of radiopharmaceuticals. Although the theranostic approach is further refined in ongoing early clinical trials (e.g. in the phase 1/2 GaLuCi™ clinical trial), the full potential of the theranostic approach in Phase 3 trials remains to be exploited in future trials.

A parallel development of the diagnostic and therapeutic radiopharmaceutical allowing a coordinated overall strategy should be the aim of both, pharmaceutical companies and the regulatory authorities, to bring these lifesaving theranostic radiopharmaceuticals to the market more quickly.

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Annex 1: Regulations and Guidelines for Radiopharmaceuticals

EU principle regulations and guidelines for radiopharmaceuticals

In Europe the European Medicines Agency (EMA) is responsible for the evaluation and supervision of pharmaceutical products. Several directives, regulations and guidelines build the legal framework for the lifecycle of pharmaceutical products, for radiopharmaceuticals in Europe these are:

- Directive 2001/83/EC (EU Medicines Directive)
  outlining the requirements for obtaining marketing authorisation, ensuring that medicinal products meet the necessary standards of quality, safety, and efficacy.
- Regulation 536/2014/EU (EU Clinical Trials Regulation)
- Regulation 726/2004/EC (EU Regulation on Medicinal Products for Human Use)
- EU Guidelines on GMP for medicinal products
  Incl. European Commission Guidelines on Good Manufacturing Practice (GMP) for Radiopharmaceuticals (Annex 3 of the EU GMP guidelines)
  ensuring the safety, quality, and efficacy of radiopharmaceuticals during the manufacturing process.
- EU Guidelines on GCP for clinical trials
  ensuring that clinical trials (of radiopharmaceuticals) are conducted ethically and in compliance with international standard)
- EMA scientific guideline on radiopharmaceuticals EMEA/CHMP/QWP/306970/2007
- Directive 2013/59/Euratom
  laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation
- Directive 2011/70/Euratom
  establishing a Community framework for the responsible and safe management of spent fuel and radioactive waste
- EURATOM Treaty (Article 30-36)
  providing guidelines on radiation protection for patients and healthcare professionals

US principle regulations and guidelines for radiopharmaceuticals

In the United States of America (USA) the Food and Drug Association (FDA) is responsible for the evaluation and supervision of pharmaceutical products. Several regulations and guidelines build the legal framework for the lifecycle of pharmaceutical products, for radiopharmaceuticals in the United States of America these are:

- Current Good Manufacturing Practice ("cGMP") regulations
  ensuring the safety, quality, and efficacy of radiopharmaceuticals during the manufacturing process.
- Federal Food, Drug, and Cosmetic Act ("FDCA") incl. the Drug Amendments of 1962 (Kefauver-Harris Amendments) = Code of Federal Regulations ("CFR") Title 21, Chapter 9 provides the framework for the approval, manufacturing, and marketing of drugs, ensuring they are safe and effective
- CFR Title 21
  - Part 211 and 212
    laying out the general (Part 211) and specific requirements (Part 212) for the manufacture of radiopharmaceuticals, including the use of radioactive materials, quality control, and labelling.
  - Part 312
    governing Investigational New Drug Applications ("INDs")
  - Part 314
    governing the New Drug Application ("NDA") process
  - Part 315
    governing Diagnostic Radiopharmaceuticals
  - Part 601 Subpart D
    governing the Licensing incl. evaluation of effectiveness and safety of diagnostic radiopharmaceuticals
- FDA guidance documents
  providing guidance on various aspects of the regulation of radiopharmaceuticals, including the development, approval, and post-approval surveillance
- Nuclear Regulatory Commission (NRC) regulations

The NRC is responsible for the safety and security of the use of radioactive materials in medicine and other industries.

- Part 35 - medical use of Byproduct Material in private practices, clinics, hospitals and government medical facilities
- Part 32 - commercial nuclear pharmacies (or radiopharmacies), manufacturers, and distributors
- Part 50 - medical isotope production

Annex 2: Marketing Authorisation Process

Marketing Authorisation Application EU

National Procedure

In the national procedure the company seeks marketing authorisation in just one EU member state. The DCP is used when a product has not yet been authorised in any EU member state. A company selects one member state to assess the application (the Reference Member State, "RMS"). Other member states (Concerned Member States, "CMS") are involved, and if there are no objections, the RMS's assessment is mutually recognised by the CMSs, leading to national authorisations in several countries approximately at the same time. The MRP is used when a product is already authorised in one EU member state (future RMS). The holder of the authorisation may apply for this authorisation to be recognised in other EU member states (CMS). This is done by submitting the existing authority assessment along with an application to other member states, which agree to recognise the validity of the original, national marketing authorisation.

Centralised Procedure

Under the centralised procedures a marketing authorisation can be obtained by seven different types of application:

Directive 2001/83/EC Article	**Type of application**
8(3)	Full or full-mixed application (complete dossier)
10(1)	Generic medicinal product application
10(3)	Hybrid medicinal product application
10(4)	Similar biologic product application
10a	Well established use application (literature only)
10b	Fixed dose combination (components already authorised separately) application
10c	Informed consent application

Table 14: Types of centralised marketing authorisations (EMA)

Full dossier or Stand-alone application

A stand-alone application requires a complete documentation of quality, safety and efficacy. Although this documentation is usually based on the applicant's own data, it is possible to substitute own data by bibliographical references [87]. This approach, called mixed application, follows the same legal requirements as set out in Article 8(3).

Well established use

Article 10a of Directive 2001/83/EC addresses the approval of medicines based on well-established use. This legal basis is significant for certain medicines, including radiopharmaceuticals, that are already known to be safe and effective due to their long-standing use in medical practice.

For a medicinal product to be approved under Article 10a, the following criteria must be met:

- Well-Established Use: The product must have a history of long-term, widespread clinical use in the EU, demonstrating consistent safety and efficacy (systematic and documented use ≥ 10 years)
- Active Substance: The active substance of the new product must be substantially similar to that in an already authorised medicinal product that has been used safely and effectively for a long period.
- No Need for New Clinical Trials: The well-established use means that detailed clinical trial data may not be necessary, as the product's safety and efficacy are already demonstrated by the medical community. However, scientific literature and data on post-market use are essential.
- Specific Documentation: Applicants must provide evidence of the product's use and clinical data, demonstrating that it meets the standards for safety, efficacy, and quality, typically relying on scientific literature rather than new clinical trials.

The above-described long-term use outside of clinical studies is feasible due to national provisions that enable an use of non-authorised radiopharmaceuticals. For example, in Germany, the AMRadV (Verordnung über radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel) §2 allows the use of diagnostic radiopharmaceuticals which are produced in-house for up to 20 patients per week without the need of a MA.

Examples for radiopharmaceuticals approved under Article 10a of Regulation (EC) No 726/2004 are discussed in Annex 3.

Companion diagnostics EMA

Until 2017, CDx were not defined in the European legislation and, as a consequence, manufacturers were allowed to self-certify CDx to obtain a Conformitè Europëene (“CE”) mark. Scientific data supporting the quality and performance of CDx have not been assessed by the notified bodies [88]. The term “Companion Diagnostics” was first implemented in the EU with the in vitro diagnostic medical device regulation (IVDR) becoming effective in May 2022. The definition laid down in article 2(7) of Regulation (EU) 2017/746 is:

"Companion diagnostic" means a device which is essential for the safe and effective use of a corresponding medicinal product to:

- identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product

Under IVDR, CDx are classified as Class C devices (the second highest risk level) and require conformity assessment by a notified body and a consultation with a medicinal products authority to assess the device's suitability for the related medicinal product. The notified body must seek a scientific opinion from the EMA if the medicinal product is under the centralised authorisation procedure, already authorised through it, or has a pending marketing authorisation application via this procedure. For medicinal products not under the centralised procedure, the notified body may consult either a national competent authority or the EMA for the scientific opinion.

Each application submitted to the EMA should consists of a cover letter, application form, e draft instructions for use (IFU) and draft summary of safety and performance (“SSP”). The consultation will be started once the notified body has performed their review as part of the conformity assessment of the device and the draft SSP and IFU have been updated accordingly.

CDx devices always require clinical evidence data including scientific validity, analytical performance and clinical performance. This performance data can be based on a) clinical performance studies; b) Concordance analysis between CDx and a gold standard method; or c) Real-world evidence [89].

New Drug Application FDA

The FDA has established various pathways for the approval of NDAs to ensure that safe and effective medications are available to the public. Among these pathways, sections 505(b)(1) and 505(b)(2) of the Federal Food, Drug, and Cosmetic Act are the most important ones.

Stand-alone applications

The 505(b)(1) pathway is the traditional route for the approval of new drugs. This process requires the submission of a full NDA, including extensive data from preclinical studies and clinical trials to demonstrate the safety and efficacy of the drug for its intended use.

Literature based approvals

Literature-based approvals refer to the process by which the FDA approves a medicinal product based on the review of existing scientific literature, rather than requiring the sponsor to conduct new clinical trials. This approach is typically applied in specific cases and under certain circumstances where adequate evidence already exists in scientific publications. The approval pathway under Section 505(b)(2) allows for a hybrid submission that combines new clinical data with data from published literature or previous findings. This section is particularly relevant for drugs approved based on literature-based evidence.

Abbreviated New Drug Applications

An abbreviated new drug application ("ANDA") contains data which is submitted to FDA for the review and potential approval of a generic drug product. The legal basis for the filing of an ANDA is laid down in section 505(j) of the Food, Drugs & Cosmetics Act. Content and format of an ANDA is described in §314.94 of the CFR. According to the FDA Homepage,

> "*Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references*"[90].

ANDAs are required to include certifications on the status of all patents applicable to the listed drug. According to section §314.94(a)12 seven different provisions are foreseen:

8. Patents claiming drug, drug product, or method of use
    I. That the patent information has not been submitted to FDA. The applicant must entitle such a certification "Paragraph I Certification"

II. That the patent has expired. The applicant must entitle such a certification “Paragraph II Certification”

III. The date on which the patent will expire. The applicant must entitle such a certification “Paragraph III Certification”

IV. That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted. The applicant must entitle such a certification “Paragraph IV Certification”. This can be based upon (1) No relevant patents, (2) Method-of-use patent, (3) Licensing agreements, (4) Untimely filing of patent information, (5) Disputed patent information or (6) Amended certifications.

PET drug ANDAs are exempt from Generic Drug User Fee Act (“GDUFA”) user fees and are subject to a 10 month GDUFA goal date [91].

Companion diagnostics FDA

The FDA defines a companion diagnostic device (“CDx”) to be either an in vitro diagnostic (“IVD”) device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product. This includes devices that monitor responses to treatment with a particular therapeutic product for the purpose for adjusting treatment in the definition of a CDx.

CDx in the US are regulated via the federal Food, Drug, and Cosmetic Act in CFR Title 21 Subchapter H Part 809 In vitro diagnostic products for human use. Unlike in the EU with the IVDR, in the US CDx are not legally defined but described in four guidances. The first document in 2014 was foundational in defining the term “Companion diagnostic” for the first time. Two years later a guidance around CDx development and regulation was published. In 2020, the FDA published group labeling guidance and in June 2023 information on the voluntary pilot program. The FDA addresses three CDx regulatory models—co-development, bridging, and follow-on – of which the first one is discussed in this thesis.

Regarding clinical trials for CDx, the FDA guidance [11] defines CDx used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm, to be considered a significant risk device under 21 CFR 812.3(m)(3) because it presents a potential for serious risk to the health, safety, or welfare of the subject, and the sponsor of the diagnostic device will be required to comply with the investigational device exemption (IDE) regulations

that address significant risk devices. CDx are by default classified as Class III medical devices and require a pre-market approval. PMA applications are comparable to the NDA process and must contain data from a registered clinical trial to ensure that the device or diagnostic is safe and effective.

Moderate-risk devices can be brought to market via the 510(k) pathway. The 510(k) regulation is found in 21 CFR 807 Subpart E and includes information required in a 510(k) which should be provided in an organized, tabulated document. There is no form for a 510(k) and the length of an application is in average 35 pages [92]. The 510(k) pathway is based on providing the FDA with documented evidence that new medical device is substantially equivalent to a predicate device that is already on the market. The FDA defines substantially equal as

> *"A claim of substantial equivalence does not mean the device(s) must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, performance, safety, effectiveness, labeling, biocompatibility, standards, and other applicable characteristics."* [93]

Clinical data might be necessary to determine substantial equivalence in the case that different indications, technological characteristics or an increased risk is anticipated [94]. Furthermore Class II products that do not have an approved equivalent product may file a "de novo" 510(k) application where review of safety and efficacy evidence is required.

Complementary diagnostics

Beside the term "Companion Diagnostic", the FDA also uses the term "Complementary diagnostics". This refers to diagnostic procedures that are recommended for the safe and effective use of a medicinal product but are not mandatory for use. In 2015, the first complementary diagnostic was approved (PD-L1 IHC 28-8 PharmDx assay) [95]. However, also used at the 2016 ASCO congress by FDA representatives and a handful of approvals in the last 10 years, the terminology is so far not part of the US legislation [88].

Of note, Complementary diagnostics are neither defined nor described in the IVDR and are not subject to any specific regulations in the EU [96].

Imaging companion diagnostics

While most CDx are in vitro diagnostic tools, to date, only one imaging CDx, FerriScan, has been approved by the FDA for measuring iron concentration in MRI. FerriScan R2-MRI Analysis

System measures the liver iron concentration and is used for the identification and monitoring of non-transfusion-dependant thalassemia patients treated with the therapeutic Deferasirox

As discussed above, CDx have been by default classified as Class III medical devices and require a pre-market approval. However, the company Resonance Health Analysis Services had requested a de novo classification for its diagnostic FerriScan R2-MRI Analysis System. The de novo classification was granted and the device was cleared as Class II device by a 510(k) as "Liver Iron Concentration Imaging Companion Diagnostic" for Deferasirox as per regulation 21 CFR 892.1001.

Combination Products FDA

Combination products are defined in 21 CFR 3.2(e). The term "Combination Product" includes:

- A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
- Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Combination products involve components that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers. Thus, they raise challenging regulatory, policy, and review management challenges. Differences in regulatory pathways for each component can impact the regulatory processes for all aspects of product

development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications [97].

Annex 3 Overview of Approved Radiopharmaceuticals in Theranostic Use

Neuroendocrine Tumors

Neuroendocrine tumors (NET) represent a heterogeneous class of diseases with large variability in aggressiveness and prognosis. NETs most frequently originate from the pancreas, the gastrointestinal tract, or the lung. A common feature of most NETs is the overexpression of somatostatin receptors (SSTRs) [98]. SSTR-based imaging using synthetic somatostatin agonists was started in 1994 with [^{111}In] In-pentetreotide (Octreoscan) being the first FDA approved and commercially marketed radiopharmaceutical [99]. Further common somatostatin agonists for clinical use are DOTA-Tyr3-Octreotate (DOTATATE), DOTA-Phe1-Tyr3-Octreotide (DOTATOC), and DOTA-NaI3-Octreotide (DOTANOC).

DOTATATE labelled with ^{68}Ga, ^{177}Lu and ^{64}Cu (Gastroenteropancreatic neuroendocrine tumors)

2016 a kit preparation for ^{68}Ga-labeling of DOTATATE (NETSPOT®, Advanced Accelerator Applications (AAA), a Novartis company, Saint-Genis-Pouilly, France) was approved by the FDA. Due to the short half-life of ^{68}Ga ($T_{1/2}$ = 68 min), on-site production or a very confined network is needed to use [^{68}Ga]-DOTATATE in the clinical routine. For this reason and despite the FDA and EMA market authorisations for [^{68}Ga]-DOTATATE and [^{68}Ga]-DOTATOC, in 2020 [^{64}Cu]-DOTATATE ($T_{1/2}$ = 12.7 h) was approved by the FDA [100].

Neither [^{68}Ga]-DOTATATE nor [^{64}Cu]-DOTATATE are approved by the EMA.

Beside Gallium and Copper, DOTATATE can also be labelled with Lutetium for therapeutic purpose. As described in the Section Public and political support of theranostic radiopharmaceuticals, Lutathera® was authorised by the European Commission in 2017 and by the FDA in 2018.

DOTATOC labelled with ^{68}Ga

A kit preparation for ^{68}Ga-labeling of DOTATOC (SomaKit TOC®, AAA, a Novartis company, Saint-Genis-Pouilly, France) was approved by the European Medicines Agency (EMA) in 2016. Additionally, [^{68}Ga]Ga-DOTATOC was approved in some European countries (Austria, Germany, and France) in 2016 (IASOtoc®, IASON GmbH, Graz, Austria).

In 2019 [^{68}Ga]Ga-DOTATOC has been approved by the FDA as the first ^{68}Ga-radiopharmaceutical for imaging of somatostatin receptor (SSTR) positive gastroenteropancreatic

neuroendocrine tumors [101]. Holder of the marketing authorisation is the UIHC–PET Imaging Center (University of Iowa Health Care (UIHC)), in Iowa, USA.

[^{68}Ga]Ga-DOTATOC is often used in a theranostic approach together with the therapeutic radiopharmaceutical [^{177}Lu]Lu-DOTATATE although both are not a true pair of identical theranostic radiopharmaceuticals since the imaging radiopharmaceutical uses the SSTR binding peptide DOTATOC, while the therapeutic radiopharmaceutical uses DOTATATE instead.

Patent situation and market exclusivity EU

In Europe, AAA holds the NDA as well as the patents for all approved radiopharmaceuticals in NETs, namely the kit preparation of [^{68}Ga]Ga-DOTATOC and [^{177}Lu]Lu-DOTATATE.

Patent situation and market exclusivity USA

[^{68}Ga]Ga-DOTATOC

While NDAs for [^{68}Ga]Ga-DOTATATE (NetSpot®) and [^{64}Cu]Cu-DOTATATE (DETECTNET®) were submitted by companies, the NDA for [^{68}Ga]Ga-DOTATOC was handed in by the academic institution University of Iowa and is not patent-protected. Building on this NDA, Evergreen Theragnostics submitted an NDA for a [^{68}Ga]Ga-DOTATOC easy-to-use kit (OCTEVY®) in December 2022. Although FDA has accepted the application for review and granted a target approval date (PDUFA date) of July 20th 2023 [102], OCTEVY® was not approved as of today (June 2025). Recently the company Lantheus acquired Evergreen Theragnostic and consequently also OCTEVY®.

[^{177}Lu]Lu-DOTATATE

In January 2024, the FDA has accepted an ANDA for [^{177}Lu]Lu-PNT2003 (Lantheus) [103], a generic formulation of [^{177}Lu]Lu-DOTATATE (Lutathera®, Novartis). This application is the first to be considered a substantially completed ANDA for lutetium [^{177}Lu]Lu-DOTATATE containing a Paragraph IV certification under the provisions of the Hatch-Waxman Act. Thus (patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted), following approval from the FDA, it is possible that [^{177}Lu]Lu-PNT2003 will be granted 180 days of marketing exclusivity in the United States. Advanced Accelerator Applications, a Novartis entity launched litigation efforts in January shortly after the FDA accepted Lantheus' generic filing for PNT2003. The argument centers on U.S. Patent No. 10.596.276, which Point/Lantheus argue is "invalid, unenforceable, and/or will not be infringed" by PNT2003, according to a complaint filed in Delaware [104].

Furthermore, in 2024, Curium seeked a 505(b)(2) NDA Approval for its own formulation of Lutetium [^{177}Lu]Lu-DOTATATE. According to the company infringement of any Orange Book listed patents is avoided [105].

Prostate cancer

Prostate Cancer is the second most diagnosed urological cancer among men worldwide. Conventional methods used for diagnosis of prostate cancer have several pitfalls including a lack of sensitivity and specificity. Furthermore, also traditional treatment methods of prostate cancer poses challenges like long-term side effects and the development of multidrug resistance [106]. Some of these pitfalls and challenges can be overcome by the use of non-invasive diagnosis and treatment of prostate cancer using appropriate radiopharmaceuticals.

Bone-targeting radiopharmaceuticals (e.g. ^{153}Sm, ^{89}Sr, and radium-223 (Xofigo, FDA approval 2013)) have been used for decades in men with metastatic prostate cancer to improve symptoms, but these compounds only localize to sites of increased bone turnover and therefore fail to deliver radiation to non-bone metastases. Further improvement in diagnosis and treatment has been achieved by the development of more sophisticated PET/CT radiopharmaceuticals, such as gallium-68 (^{68}Ga)-labelled prostate specific membrane antigen (PSMA) ligands. Thus, it is now possible to stage, localise, and choose patients for PSMA-targeted molecular radiotherapy.

PSMA ligands labeled with ^{68}Ga, ^{18}F and ^{177}Lu

PSMA-11 ([^{68}Ga]Ga—gozetoide)

[^{68}Ga]Ga-PSMA-11 was approved in the US by the FDA as the first ^{68}Ga-radiopharmaceutical for the PET imaging of PSMA-positive prostate cancer in 2020. This diagnostic radiopharmaceutical was developed by academia, the holders of marketing authorisations are the University of California Los Angeles (UCLA) Biomedical Cyclotron Facility (Los Angeles, CA, USA) and the University of California San Francisco (UCSF) Radiopharmaceutical Facility (San Francisco, CA, USA). Beside these two non-commercial FDA approvals, also the companies Telix in 2021 (Illuccix®) and AAA in 2022 (Locametz®) received approval for [^{68}Ga]Ga-PSMA-11 in the US. Also in 2022, Novartis receives European Commission approval for Pluvicto® ([^{68}Ga]Ga-PSMA-11).

PSMA-617 ([^{177}Lu]Lu-vipivotide tetraxetan)

The radiolabeled therapeutic drug [^{177}Lu]Lu-PSMA-617 [34], developed by Advanced Accelerator Applications USA, a Novartis company, was approved in the US in 2022. In the EU Pluvicto® was approved in 2022 and is marketed by Novartis AG. PSMA-617 can be labeled either with ^{68}Ga or ^{177}Lu, providing exactly the same structure for diagnosis and therapy. However, due to its wide application for the PET imaging of prostate cancer, the FDA-approved [^{68}Ga]Ga-PSMA-11, which has a similar structure, is preferred, particularly because, as described above, several kit preparations have been approved by the FDA.

18F-rhPSMA-7.3 (^{18}F-Flotufolastat)

^{18}F-Flotufolastat (POSLUMA®) [38,107] is an ^{18}F-labelled radiohybrid (rh) PSMA-targeted imaging drug being developed by Blue Earth Diagnostics. In 2023, ^{18}F-flotufolastat received its first approval in the USA. It is not approved for use by the European Commission.

^{18}F-DCFPyL (^{18}F-Piflufolastat)

^{18}F-Pifufolastat [35,108] is an ^{18}F-labelled diagnostic imaging drug that has been developed by Progenics Pharmaceuticals Inc. ^{18}F-Pifufolastat was approved by the FDA in the USA in 2021 (PYLARIFY®) and by the European Commission in 2023 (PYLCLARI®) with Curium as MAH.

Furthermore, therapeutic PSMA-targeting radiopharmaceuticals labelled with ^{131}I and ^{225}Ac are under development.

L-leucine derivativ labelled with ^{18}F (^{18}F-Fluciclovine)

L-type amino acid transporter (LAT1) and the sodium-dependent neutral amino acid transporter (ASCT2), up-regulated in many human cancers, including PCa [109]. As there is currently no therapeutic radiopharmaceutical targeting LAT1 approved by FDA or EMA, ^{18}F-Fluciclovine (Axumin) will not be discussed further in the following Chapters.

Patent situation and market exclusivity EU and US

[^{68}Ga]Ga-PSMA-11

[^{68}Ga]Ga-PSMA-11 was developed by two academic institutions which waived exclusivity and opened the market to both academia and industry to submit abbreviated NDAs. Thus there are several [^{68}Ga]Ga-PSMA-11 products on the market.

In February 2023, Beforpharma and University of Bari received national patent (with international extension) for a technology of cold kit based on PSMA ligands for the preparation of

radiopharmaceutical, in particular [^{68}Ga]Ga-PSMA-11. The invention was developed by group of researchers from University of Bari, Department of Pharmacy and Beforpharma.

[^{177}Lu]Lu-PSMA-617

Philip Low, Purdue University College of Science, led the research leading to the invention of [^{177}Lu]Lu-PSMA-617. The ownership of the PSMA-617 patent was asserted in 2018 by Molecular Insight Pharmaceuticals, Inc., a subsidiary of Progenics [110]. The patent was previously exclusively licensed to ABX GmbH, and thereafter sub-licensed to Endocyte, Inc., which was acquired by Novartis. After several years of legal disputes, a global settlement agreement was found including $24.0 million lump sum payment to Progenics and reimburse of Progenics for certain fees and expenses in connection with the litigation by Novartis [110]. These patent disputes and changes led to temporary shortages in the supply of PSMA-617 [29].

Novartis holds a patent regarding PSMA-binding conjugates and related pharmaceutical formulations and methods to treat prostate cancer (U.S. Patent 10,624,970). Together with the Purdue Research Foundation filed a lawsuit regarding PNT-2002 infringing the U.S. patent against Point Biopharma [111].

Breast cancer

Synthetic derivative of estradiol (^{18}F-Fluoroestradiol)

^{18}F-Fluoroestradiol binds to the estrogen receptor and thereby concentrates within ER-expressing cells. Estrogen receptor is a key oncogenic driver in the majority of breast cancer and is expressed in approximately 80% of all breast cancer patients. As there is currently no therapeutic radiopharmaceutical targeting the estrogen receptor approved by FDA or EMA, ^{18}F-Fluoroestradiol will not be discussed further in the following Chapters.

Annex 4: Designation of EU and US Approvals

Designations for drug development and accelerated approval pathways in the EU

The EU has created specialized pathways to accelerate the development and approval of promising new therapies, especially those addressing unmet medical needs or serious conditions.

The EMA offers the following pathways to expedite drug development and approval:

	Purpose	Eligibility	Benefit	Regulation
Orphan Drug Designation (ODD)	Provides incentives for developing drugs for rare diseases	Rare diseases (affecting fewer than 5 in 10,000 people in the EU)	10 years of market exclusivity, fee reductions, and access to grants	Regulation (EC) No 141/2000
Conditional Marketing Authorisation (CMA)	For drugs that address unmet medical needs (e.g., rare or life-threatening diseases) where comprehensive data might not yet be available	Benefits of the drug outweigh the risks based on the available data, with the obligation to complete additional studies after approval, CMA valid for 1 year	Non-standard MA based on a dossier containing less than comprehensive data	Regulation (EC) No 726/2004 Article 14(7)
Marketing Authorisation under exceptional circumstances	For drugs that address unmet medical needs (e.g., rare or life-threatening diseases) where comprehensive data is not expected	- indication so rare that the applicant cannot reasonably be expected to provide comprehensive evidence; **or** - in present state of scientific knowledge, comprehensive data cannot be provided; **or** • contrary to ethical principles to collect the information	Non-standard MA based on a dossier containing less than comprehensive data	Regulation (EC) No 726/2004 Article 14 (8)
Accelerated Assessment	Speeds up the review process for	drugs that address a serious condition and provide a significant improvement over existing treatments.	A standard review time of 150 days, reduced from the usual 210 days.	Regulation (EC) No 726/2004
PRIME (PRIority MEdicines) Scheme	Designed to enhance support for the development of medicines that target an unmet medical need.	drugs with the potential to significantly improve the treatment of conditions with no adequate treatment options	Early and more frequent scientific advice, direct access to EMA services, and a possibility of accelerated assessment.	Regulation (EC) No 726/2004

Table 15: Pathways to expedite drug development and approval (EMA)

From the above discussed designations for accelerated development, up to now, only accelerated approval and orphan drug designation have been granted to the approved radiopharmaceuticals. While none of the already approved radiopharmaceuticals were granted PRIME status, currently (status from 23.02.25) 2 radiopharmaceuticals under development have a PRIME status. The therapeutic radiopharmaceutical, currently in Phase 3, iopofosine I 131 (CLR 131) and the diagnostic radiopharmaceutical [^{68}Ga]Ga-boclatixafortide ([^{68}Ga]Ga-PentixaFor), also in a Phase 3 status [112].

Radiopharmaceutical	Dx/Tx	Designation	ODD	Marketing authorisation holder (MAH)
GEP-NETs				
[^{68}Ga]Ga-DOTATOC (SomaKit TOC®)	Dx	---	ODD (03/15)	AAA (Novartis)
[^{177}Lu]Lu-DOTATATE (Lutathera®)	Tx	Accelerated assessment	ODD (07/17)	AAA (Novartis)
PSMA positive prostate cancer				
[^{68}Ga]Ga-PSMA-11 (Locametz®)	Dx	---	---	Novartis
^{18}F-piflufolastat (PYLCLARI®)	Dx	---	---	Curium
[^{177}Lu]Lu-PSMA-617 (Pluvicto®)	Tx	---	---	Novartis

AAA: Advanced Accelerator Applications; Dx: Diagnostics; ODD: Orphan Drug Designation; Tx: Therapeutics

Table 16: Designations and review modalities of theranostic radiopharmaceuticals approved by the EMA

Designations for drug development and accelerated approval pathways in the US

For drugs that treat serious conditions with unmet medical needs, the FDA has special programs like fast-track or accelerated approval**.** These programs aim to speed up the approval process, especially for life-threatening diseases like cancer.

Designation	Eligibility	Benefit	Legal Basis
Fast Track	- drugs intended to treat serious or life-threatening diseases - data demonstrate potential to address unmet medical need	- rolling review - expedited development (i.e. more interaction with FDA)	Section 351(a)(3) or 505(i) of FDASIA amending FD&C Act
Breakthrough Therapy	- drugs intended to treat serious or life-threatening diseases	- rolling review - intensive guidance from FDA	Section 902 of FDASIA amending FD&C Act

	- Clinical data suggest more effective than existing therapies		
Accelerated Approval	Drugs that fill unmet need for serious conditions	Approval based on surrogate endpoints	Section 901 of FDASIA amending FD&C Act
Priority review	- priority review voucher - drugs that offer major advances in treatment - drugs for conditions with no existing adequate treatment	Expedited NDA review (6 month vs. normal 10 month)	Prescription Drug User Fee Act (PDUFA)
Orphan Drug	- Condition affecting fewer than 200,000 persons in the US OR - Drugs that will not be profitable within 7 years following approval	- Tax credits for qualified clinical trials - Exemption from user fees - Potential seven years of market exclusivity after approval	21 CFR Part 316 Orphan Drug Act in 1983

Table 17: Pathways to expedite drug development and approval (FDA)

US approvals	Dx/Tx	Review modality	ODD	Designations	Company
GEP-NETs					
[^{68}Ga]Ga-DOTATATE (NetSpot®)	Dx	Priority Review	ODD (12/13)	---	AAA (Novartis)
[^{68}Ga]Ga-DOTATOC	Dx	Standard	ODD (10/13)	---	University Iowa
[^{64}Cu]Cu-DOTATATE (DETECTNET®)	Dx	Priority Review; Rolling review	ODD (05/16)	Fast track (12/18)	Radiomedix
[^{177}Lu]Lu-DOTATATE (Lutathera®)	Tx	Priority Review; Rolling review	ODD (01/09)	Fast track (04/15)	AAA (Novartis)
PSMA positive prostate cancer					
[^{68}Ga]Ga-PSMA-11	Dx	Standard	---	---	UCSF Radiopharmaceutical Facility
[^{68}Ga]Ga-PSMA-11	Dx	Standard	---	---	UCLA Radiopharmaceutical Facility
^{18}F-flotufolastat (Posluma®)	Dx	Standard	---	---	Blue Earth Diagnostics
^{18}F-piflufolastat (PYLARIFY®)	Dx	Priority Review	---	---	Progenics Pharmaceuticals
[^{68}Ga]Ga-PSMA-11 (Illuccix®)	Dx	Standard	---	---	Telix Pharmaceutical
[^{68}Ga]Ga-PSMA-11 (Locametz®)	Dx	Standard	---	---	AAA (Novartis)
[^{177}Lu]Lu-PSMA-617 (Pluvicto®)	Tx	Priority Review	---	BTD (06/21)	AAA (Novartis)

AAA: Advanced Accelerator Applications; BTD: Breakthrough designation; Dx: Diagnostics; ODD: Orphan Drug Designation; Tx: Therapeutics; UCSF: University of California, San Francisco; UCLA: University of California, Los Angeles

Table 18: Designations and review modalities of theranostic radiopharmaceuticals approved by the FDA

Annex 5: Radiopharmaceuticals under Investigation for Theranostic Use

	Therapeutic RP	Isotope	Corresp. diagnostic RP	Status Diagnostic RP
Phase 3	AAA-817	^{225}Ac	PSMA targeted	approved
	Iopofosine	^{131}I	PSMA targeted	Approved
	PNT2002	^{177}Lu	PSMA targeted	Approved
	PSMA I&T	^{177}Lu	PSMA targeted	Approved
	TLX591	^{177}Lu	PSMA targeted	Approved
	ITM-11	^{177}Lu	SSTR targeted	Approved
	PNT2003	^{177}Lu	SSTR targeted	Approved
	RYZ101	^{225}Ac	SSTR targeted	Approved
	Iomab-B	^{131}I	---	N/A
Phase 2	**DEBIO0228**	**^{177}Lu**	**^{68}Ga-DEBIO0328**	**Theranostic Phase 1/2**
	FAP-2286	**^{177}Lu**	**[^{68}Ga]Ga FAP-2286**	**Theranostic Phase 1/2**
	FPI-1434	**^{225}Ac**	**[^{111}In]-FPI-1547 (SPECT)**	**Theranostic Phase 1/2**
	NeoB	**^{177}Lu**	**[^{68}Ga]Ga-NeoB**	**Theranostic Phase 1/2**
	SAR-BBN	^{67}Cu	[^{64}Cu]Cu-SAR-BBN	Completed Phase 2
	SAR-bisPSMA	^{67}Cu	[^{64}Cu]Cu-SAR-bisPSMA	Ongoing Phase 3
	SARTATE	^{67}Cu	[^{64}Cu]Cu-SARTATE	Completed Phase 2
	TLX66	^{90}Y	^{99m}Tc-besilesomab (SPECT)	Approved
	TLX101	^{131}I	[^{18}F]FET (Pixclara)	CRL (04/2025)
	TLX250	^{177}Lu	^{89}Zr-DFO-girentuximab	PDUFA date 27.08.25
	VMT01	**^{212}Pb**	**[^{68}Ga]-VMT02 [^{203}Pb]-VMT01 (SPECT)**	**Completed Phase 1 + Theranostic Phase 1/2**
	AB001		PSMA targeted	N/A
	ADVC-001	^{212}Pb	PSMA targeted	N/A
	CONV01-alpha	^{225}Ac	PSMA targeted	N/A
	FL-020	^{225}Ac	PSMA targeted	N/A
	FPI-2265	^{225}Ac	PSMA targeted	N/A
	LNTH-1095	^{131}I	PSMA targeted	N/A
	PNT2001	^{225}Ac	PSMA targeted	N/A
	PSMA-R2 (AAA602)	^{177}Lu	PSMA targeted	N/A
	PSMA-R2	^{225}Ac	PSMA targeted	N/A
	rhPSMA10.1	^{177}Lu	PSMA targeted	N/A
	Alphamedix	^{212}Pb	SSTR targeted	N/A
	VMT-a-NET	^{212}Pb	SSTR targeted or [^{203}Pb]VMT-a-NET	N/A
	Actimab-A	^{225}Ac	---	N/A
	CAM-H2	^{131}I	---	N/A

Phase 1	BAY3563254	^{225}Ac	PSMA targeted	N/A
	BAY3546828	^{225}Ac	PSMA targeted	N/A
	LNC1003	^{177}Lu	PSMA targeted	N/A
	TLX592	^{67}Cu	PSMA targeted	N/A
	FPI-2059	^{225}Ac	[^{111}In]-FPI-2058	Theranostic Phase 1
	FPI-2068	^{225}Ac	[^{111}In]-FPI-2107	Theranostic Phase 1
	LNC1004	^{177}Lu	^{68}Ga-FAPI-46	Completed Phase 2
	LNTH-2503	^{177}Lu	^{68}Ga-LNTH-2503	Theranostic Phase 1
	PentixaTher	^{177}Lu/^{90}Y	^{68}Ga-PentixaFor	Phase 3
	PNT2004 PNT6555	^{225}Ac/^{177}Lu	Ga-PNT6555	Theranostic Phase 1
	SSO-110	^{225}Ac	^{68}Ga-SSO120	Theranostic Phase 1/2
	FF-21101	^{90}Y	---	N/A
	GRPR	^{212}Pb	---	N/A
	RAD204	^{177}Lu	---	N/A
	SADA-PRIT	^{177}Lu	---	N/A

Table 19: Theranostic radiopharmaceuticals (RPs) under development (05/2025)

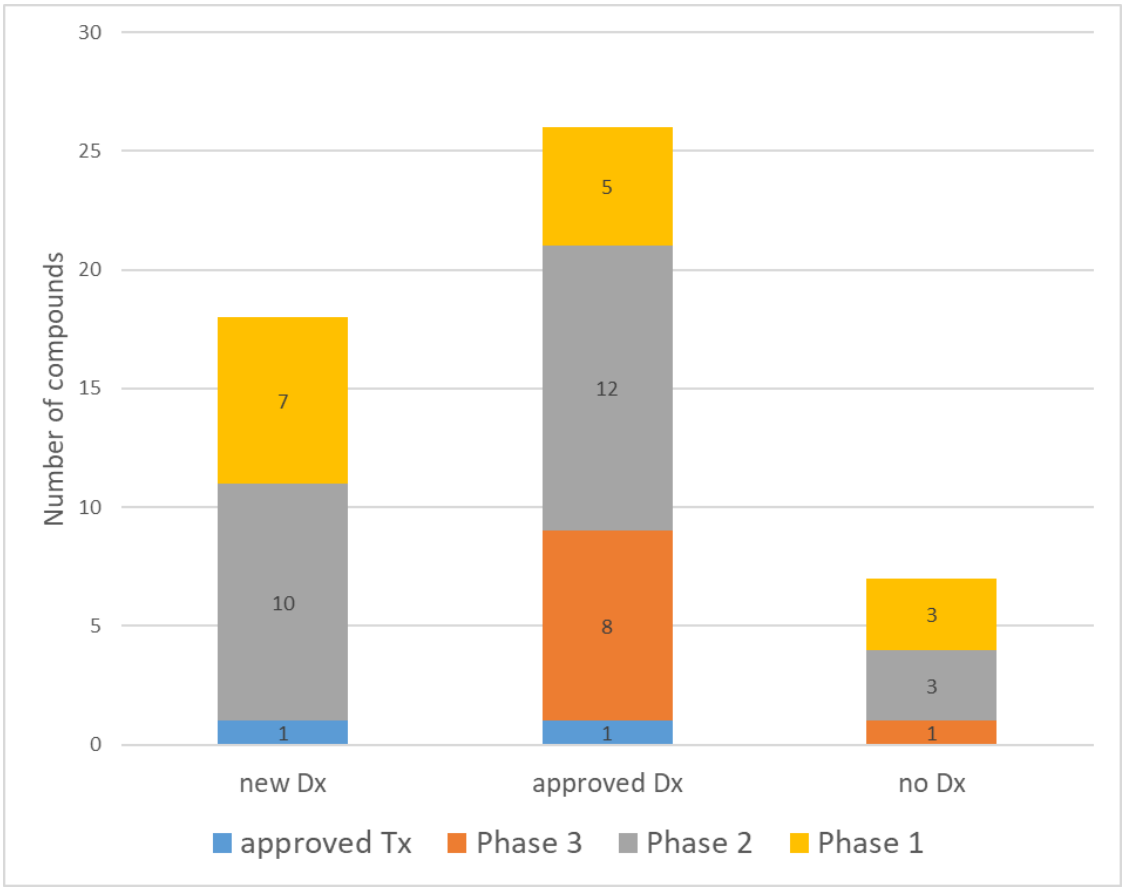


Figure 4: Diagnostic Radiopharmaceuticals relating to therapeutic radiopharmaceuticals currently under development (05/2025)

Annex 5: Radiopharmaceuticals under Investigation for Theranostic Use

	Phase	Trial name	Location	Target patient No	Sponsor	Indication
Target: Carbonic Anhydrase IX (CA IX)						
[^{177}Lu]Lu-DPI-4452	I/II	GaLuCi™	FR, AUS	155	Debiopharm	Solid tumors
^{89}Zr-TLX250	III	ZIRCON	US, AUS, EU, UK	300	Telix	renal cell carcinoma
	Further studies Phase I and II		AUS, US, JPN, EU	---	academia	several
[^{177}Lu]Lu-TLX250	I	---	AUS	36	Telix	CA-IX expressing solid tumors
Target: Fibroblast activation protein						
[^{177}Lu]Lu and [^{68}Ga]Ga-FAP 2286	I/II	LuMIERE	US	222	Novartis	Solid tumors
[^{68}Ga]Ga-and [^{64}Cu]Cu-FAP-2286	I	---	US	116	UCSF, San Francisco	Solid tumors
[^{68}Ga]Ga-FAP-2286	I	---	US	30	UCSF, San Francisco	Pathologic fibrosis
Target: Gastrin-releasing peptide receptor (GRPR)						
[^{68}Ga]Ga-NeoB	II	---	AUS	20	St Vincent's Hospital, Sydney	Breast cancer
[^{177}Lu]Lu-NeoB	I/II		US, AUS	58	Novartis	Breast cancer
[^{64}Cu]Cu-SAR-Bombesin	II	SABRE	US	30	Clarity	Prostate Cancer
	I/II	COMBAT	US	38	Clarity	Prostate Cancer
Target: LAT-1						
[^{18}F]FET-TLX101-CDx (Pixclara)	NDA	---	US	Expanded Access	Telix	Glioblastoma
TLX101-Tx	I (finalized)	IPAX-1 IPAX-2	EU, AUS	10 12	Telix	Glioblastoma
[^{18}F]FET	19 further studies Phase I or II		US, EU	---	academia	Several
Target: CD66						
^{99}mTc-besilesomab (Scintimun)	Approved in EU				CIS bio international	Inflammation/infection in peripheral bone in suspected osteomyelitis

TLX66 (^{90}Y-DTPA-be-silesomab)	II	NCT04856215	UK	25	Great Ormond Street Hospital for Children NHS Foundation Trust	Pediatric Leukemia
	II	NCT00637767	UK	25	University of Southampton	Multiple Myeloma
	I	NCT04082286	UK	9	Great Ormond Street Hospital for Children NHS Foundation Trust	Pediatric Leukemia
	I/II	NCT01521611	UK	62	Univ. Hospital Southampton NHS Foundation Trust	HSCT for Poor Risk Haematological Malignancy
Target: IGF-1R						
[^{225}Ac]-FPI-1434	I/II	NCT03746431	US, AUS, CA	253	Fusion Pharmaceuticals Inc.	Solid tumors
Target: Melanocortin sub-type 1 receptor (MC1R)						
[^{212}Pb]VMT01	I/II		US	264	Perspective Therapeutics	Melanoma
Target: SSTR2						
[^{67}Cu]Cu SARTATE	I/II	NCT03936426	AUS	5	Clarity Pharmaceuticals Ltd	Meningioma
	I/II	NCT04023331	US	34	Clarity Pharmaceuticals Ltd	Pediatric Neuroblastoma
[^{64}Cu]Cu-SARTATE	I	NCT04440956	No info	10	Clarity Pharmaceuticals Ltd	NET
	II	NCT04438304	No info	45	Clarity Pharmaceuticals Ltd	NET

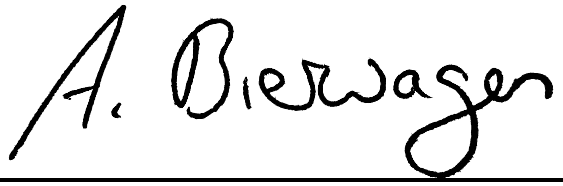
AUS: Australia; CA: Canada; EU: EU; JPN: Japan; NET: Neuroendocrine tumors; UK: United Kingdom; US: United States of America;

Table 20: Selection of ongoing theranostic clinical trials (only data from US, EU, CAN, UK and AUS)

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Rimpar, den 16.06.2025



Dr. Alessandra Bierwagen