White paper

The Dutch innovation ecosystem for nuclear medicine

Recommendations to improve innovativeness and earning capacity to become a European hotspot for nuclear medicine

March 2024

FAST

Colophon

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The Dutch innovation ecosystem for nuclear medicine
Recommendations to improve innovativeness and earning capacity to become a European hotspot for nuclear medicine

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List of abbreviations

ACMUI	Advisory Committee on The Medical Use of Isotopes
ANSTO	Australian Nuclear Science and Technology Organisation
ANVS	Authority for Nuclear Safety and Radiation Protection
API	Active Pharmaceutical Ingredient
ARTnet	Australian Radiopharmaceutical Trials Network
BSS(D)	Basic Safety Standards (Directive)
CBG	Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen)
COVRA	Manages radioactive waste in the Netherlands
CRO	Contract Research Organisation
CT	Clinical Trial
CTR	Clinical Trials Regulation
DOT	U.S. Department of Transportation
EANM	European Association of Nuclear Medicine
EFOMP	European Federation of Organisations for Medical Physics
EMA	European Medicines Agency
ESA	Euratom Supply Agency
EC	European Commission
EuChemS	European Chemical Society
EU	European Union
FACA	Federal Advisory Committee Act
FAST	Centre for Future Affordable Sustainable Therapies Development
FDA	U.S. Food and Drug Administration
GnW	Dutch Medicines Act
HCPs	Healthcare Practitioners
HFR	High Flux Reactor
HTA	Health Technology Assessment
IRRS	Evaluation of nuclear safety and radiation protection systems
IP	Intellectual Property
MIT	Small and Medium-sized Enterprise Innovation Stimulation Top Sector Program (MKB Innovatie Stimulering Topsectoren)
MV	Mega Volt
NMEU	Nuclear Medicine Europe
NRC	Nuclear Regulatory Commission

NRG	Nuclear Research and Consultancy Group
NFIA	Netherlands Foreign Investment Agency
NGF	National Growth Fund
NKI	Netherlands Cancer Institute
NKRV	Netherlands Clinical Radiochemistry Association
NMR	Nuclear Magnetic Resonance
NRC	Nuclear Regulatory Commission
NVKF	Dutch association for clinical physicists
NVMO	Netherlands Association for Medical Oncology
NVNG	Dutch Association for Nuclear Medicine
NVU	Netherlands Association for Urology
NVvR	Netherlands Association for Radiology
NVZA	Netherlands Association of Hospital Pharmacists
PET	Positron Emission Tomography
PHMSA	Pipeline and Hazardous Materials Safety Administration
PSMA	Prostate-specific membrane antigen
PSMAForum	Prostate-specific membrane antigen Forum
R&D	Research and Development
RIVM	National Institute for Public Health and the Environment
ROMs	Regional Development Funds
RTO	Research and Technology Organisation
SAMIRA	Strategic Agenda for Medical Ionising Radiation Applications
SHINE	Subcritical Hybrid Integrated Neutron Emitter
SMEs	Small and Medium-sized Enterprises
SPECT	Single-Photon Emission Computed Tomography
TU Delft	Delft University of Technology
US(A)	United States (of America)
VTGM	Voor Toediening Gereed Maken (prepare for administration)
VFF	Early-Stage Financing
VWS	Dutch Ministry of Health, Welfare and Sport
WBSO	Research and Development Allowance (Wet Bevordering Speurwerk en Ontwikkeling)
WMO	Legislation protecting participants in clinical research in the Netherlands
ZIN	National Health Care Institute
Zvw	Legislation governing healthcare insurance in the Netherlands

Management summary

This report is prepared by Technopolis Group on request of the Centre for Future Affordable Sustainable Therapies Development (FAST) to provide insight into the current Dutch innovation ecosystem for nuclear medicine and recommendations to improve this ecosystem. Opportunities to increase the earning capacity for the Netherlands and opportunities to strengthen the innovativeness of this Dutch ecosystem are addressed in the recommendations. These should contribute to an innovation ecosystem in which radiopharmaceuticals are efficiently developed, making them available faster to patients against an acceptable price.

Based on their study, Technopolis concludes that the Dutch innovation ecosystem for nuclear medicine is a strong ecosystem that holds a great promise and is well-known internationally. However, more collaboration and coordination are required to unlock the full potential of this ecosystem. Coordination should provide a shared direction and prioritisation of actions to improve the innovation ecosystem for nuclear medicine. Collaboration – within nuclear medicine, with other medical disciplines and between research, hospitals, industry, and government – should improve the development process of radiopharmaceuticals.

The strengths of the innovation ecosystem for nuclear medicine are its completeness in terms of actors, its high-quality – and in some respects even unique – facilities, its international connectedness and reputation, and the quality of research conducted. The weaknesses of this innovation ecosystem are in regulation, available funding (for research and valorisation), human capital and education (for radiation protection and nuclear medicine physicians) and taking risk (mainly entrepreneurship and investment).

The development process of radiopharmaceuticals, from idea to use of these medicines, can be improved in the Netherlands. Although Dutch research in nuclear medicine is strong, the valorisation of this research and the translation into further phases of clinical trials is low. In the development process, most challenges are experienced during clinical trials. Also, market access is considered a barrier in the Netherlands, in part due to more restrictive Dutch regulations as well as national requirements and procedures for expensive medicines.

The Netherlands has internationally a strong reputation in nuclear medicine and is at the forefront in Europe. Still lessons can be learned from other regions. In terms of organisation, the EU innovation ecosystem for nuclear medicine seems to be better organised at high level. Also, Australia is a good example for collaboration, where a radiopharmaceutical trials network was set up to improve collaboration and to upscale clinical trials in nuclear medicine. This collaboration, in combination with favourable regulation and funding for investigator-led clinical trials, have spurred innovation in nuclear medicine in Australia. The USA is not just very strong in nuclear medicine research and clinical trials, it is also an example in terms of collaboration with businesses and its (generally) simpler regulatory framework. The business mindset in the USA contributes to valorisation and a focus on unmet clinical need.

The field and role of nuclear medicine is internationally changing with the development and market entry of recent radiopharmaceuticals and therapies. To have patients benefit from these developments and to maintain a frontrunners position, actions are needed to strengthen the Dutch innovation ecosystem for nuclear medicine. With these investments, the Netherlands can capitalise on recent public and private investments in new facilities in the ecosystem. The timing to do that is now, as the Dutch National Growth fund provides opportunities for investments and the Dutch and European governments are currently supportive towards nuclear medicine.

Technopolis recommends the following actions to improve the innovativeness of the Dutch innovation ecosystem for nuclear medicine:

- Organise the innovation ecosystem for nuclear medicine by creating a platform in which academia, hospitals, industry, government, and patient organisations meet to collaborate to i) address challenges in the ecosystem, ii) prioritise actions to strengthen the ecosystem and iii) streamline R&D.
- Complement the platform with a network of a few innovation centres for nuclear medicine across the Netherlands, located at existing hotspots for nuclear medicine. Such innovation centres could be in or near (academic) hospitals or sites where medical isotopes are produced.
- Focus/coordinate investigator-led R&D activities and actions by developing a shared roadmap with this platform. This roadmap should set shared goals and priorities for Dutch investigator-led R&D in nuclear medicine based on unmet medical needs.
- Commit public and private investments to this roadmap. All actors involved should be committed to the roadmap to make it a success. The Dutch National Growth Fund could be a funding opportunity for these investments.
- Use the platform to engage with competent authorities and involved ministries to discuss procedural and regulatory barriers with the aim to reduce those barriers within the scope of existing EU legal frameworks.

Technopolis recommends the following actions to improve the earning capacity of the Dutch innovation ecosystem for nuclear medicine:

- Improve the valorisation/translation of R&D in nuclear medicine by organising dedicated valorisation support at the recommended innovation centres.
- Market the Dutch ecosystem for nuclear medicine better in the Netherlands and abroad to attract businesses, talent, and investments.
- Address, as a platform, human capital needs and requirements with (higher) education providers. Future demand for human capital should be articulated to these education providers to better match demand and supply on the labour market.
- Strengthen the demand side for nuclear medicine. Ensuring novel nuclear medicine therapies can be provided to patients increases the earning capacity from a societal (better healthcare) and economic perspective (if Dutch businesses involved), but requires investments in hospital infrastructure and facilities.

FAST should facilitate that the proposed recommendations are addressed by the stakeholders of the ecosystem, for example in the proposal of the DECISIVE consortium and the roadmap of the quatermaster for medical isotopes.

Managementsamenvatting

Dit rapport is opgesteld door Technopolis Group op verzoek van het Centre for Future Affordable Sustainable Therapies Development (FAST) om inzicht te geven in het huidige Nederlandse innovatie-ecosysteem voor nucleaire geneeskunde en om aanbevelingen te doen om dit ecosysteem te verbeteren. Kansen om het verdienvermogen voor Nederland te vergroten en kansen om de innovatiekracht van dit Nederlandse ecosysteem te versterken, komen in de aanbevelingen aan de orde. Deze moeten bijdragen aan een innovatie-ecosysteem waarin nucleaire geneeskunde efficiënt wordt ontwikkeld, waardoor ze sneller beschikbaar zijn voor patiënten tegen een aanvaardbare prijs.

Op basis van hun onderzoek concludeert Technopolis dat het Nederlandse innovatie-ecosysteem voor nucleaire geneeskunde een sterk ecosysteem is dat veelbelovend is en internationaal bekend is. Er is echter meer samenwerking en coördinatie nodig om het volledige potentieel van dit ecosysteem te benutten. Coördinatie moet zorgen voor een gedeelde richting en prioritering van acties om het innovatie-ecosysteem voor nucleaire geneeskunde te verbeteren. Samenwerking – binnen de nucleaire geneeskunde, met andere medische disciplines en tussen onderzoeksinstellingen, ziekenhuizen, industrie en overheid – moet het ontwikkelingsproces van nucleaire geneeskunde verbeteren.

De sterke punten van het innovatie-ecosysteem voor nucleaire geneeskunde zijn de volledigheid in termen van actoren, de hoogwaardige – en in sommige opzichten zelfs unieke – faciliteiten, de internationale verbondenheid en reputatie, en de kwaliteit van het uitgevoerde onderzoek. De zwakke punten van dit innovatie-ecosysteem liggen in de regelgeving, de beschikbare financiering (voor onderzoek en valorisatie), het menselijk kapitaal en onderwijs (op het gebied van stralingsbescherming en in de nucleaire geneeskunde) en het nemen van risico's (vooral ondernemerschap en investeringen).

Het ontwikkelingsproces van nucleaire geneeskunde, van idee tot gebruik van deze medicijnen, kan in Nederland worden verbeterd. Hoewel het Nederlandse onderzoek in de nucleaire geneeskunde sterk is, is de valorisatie van dit onderzoek en de vertaling naar verdere fasen van klinische studies laag. In het ontwikkelingsproces worden de meeste uitdagingen ervaren tijdens klinische onderzoeken. Ook wordt markttoegang in Nederland als een barrière beschouwd, mede door strengere Nederlandse regelgeving en nationale eisen en procedures voor dure geneesmiddelen.

Nederland heeft internationaal een sterke reputatie op het gebied van nucleaire geneeskunde en loopt voorop in Europa. Toch kunnen er lessen worden getrokken uit andere regio's. Qua organisatie lijkt het innovatie-ecosysteem van de EU voor nucleaire geneeskunde op hoog niveau beter georganiseerd te zijn. Ook Australië is een goed voorbeeld van samenwerking, waar een netwerk voor klinische studies met nucleaire geneeskunde werd opgezet om de samenwerking in en de opschaling van klinische proeven in de nucleaire geneeskunde te verbeteren. Deze samenwerking, in combinatie met gunstige regelgeving en financiering voor door onderzoekers geleide klinische onderzoeken, heeft innovatie in nucleaire geneeskunde in Australië gestimuleerd. De VS is niet alleen zeer sterk op het gebied van onderzoek naar nucleaire geneeskunde en klinische proeven, het is ook een voorbeeld op het gebied van samenwerking met bedrijven en het (over het algemeen) eenvoudigere regelgevingskader. De *business mindset* in de VS draagt bij aan valorisatie en een focus op onvervulde klinische behoeften.

Het vakgebied en de rol van nucleaire geneeskunde verandert internationaal met de ontwikkeling en marktintroductie van recente nucleaire medicijnen en therapieën. Om patiënten te laten profiteren van deze ontwikkelingen en een koploperspositie te behouden, zijn acties nodig om het Nederlandse innovatie-ecosysteem voor nucleaire geneeskunde te versterken. Met deze investeringen kan Nederland profiteren van recente publieke en private investeringen in nieuwe infrastructuur in het ecosysteem. De timing om dat te doen is nu, aangezien het Nationaal Groeifonds kansen biedt voor investeringen en de Nederlandse en Europese overheden momenteel faciliterend optreden op het gebied van nucleaire geneeskunde.

Technopolis beveelt de volgende acties aan om de **innovatiekracht** van het Nederlandse innovatie-ecosysteem voor nucleaire geneeskunde te verbeteren:

- Organiseer het innovatie-ecosysteem voor nucleaire geneeskunde door een platform te creëren waarin onderzoekers, ziekenhuizen, industrie, overheid en patiëntenorganisaties elkaar ontmoeten om samen te werken om i) uitdagingen in het ecosysteem aan te pakken, ii) prioriteit te geven aan acties om het ecosysteem te versterken en iii) R&D te stroomlijnen.
- Vul het platform aan met een netwerk van enkele innovatiecentra voor nucleaire geneeskunde verspreid over Nederland, gevestigd op bestaande hotspots voor nucleaire geneeskunde. Dergelijke innovatiecentra kunnen zich in of nabij (academische) ziekenhuizen bevinden of locaties waar medische isotopen worden geproduceerd.
- Focus/coördineer door onderzoekers geleide R&D-activiteiten en -acties door een gedeelde roadmap met dit platform te ontwikkelen. Deze roadmap moet gedeelde doelen en prioriteiten stellen voor door Nederlandse onderzoekers geleide R&D in nucleaire medicijnen op basis van onvervulde medische behoeften.
- Verbindt publieke en private investeringen aan deze roadmap. Alle betrokken actoren moeten zich inzetten voor de roadmap om er een succes van te maken. Het Nationaal Groeifonds zou een kans kunnen zijn voor deze investeringen.
- Gebruik het platform om met de bevoegde autoriteiten en ministeries in gesprek te gaan over procedurele en regelgevende belemmeringen, met als doel die belemmeringen binnen het de bestaande EU-rechtskaders te verminderen.

Technopolis beveelt de volgende acties aan om het **verdienvermogen** van het Nederlandse innovatie-ecosysteem voor nucleaire geneeskunde te verbeteren:

- Verbeter de valorisatie/translatie van R&D in de nucleaire geneeskunde door specifieke valorisatieondersteuning te organiseren in de aanbevolen innovatiecentra.
- Zet het Nederlandse ecosysteem voor nucleaire geneeskunde beter in de markt in binnen- en buitenland om bedrijven, talent en investeringen aan te trekken.
- Ga als platform in gesprek met aanbieders van (hoger) onderwijs over de behoefte en vereisten aan menselijk kapitaal. De toekomstige vraag naar menselijk kapitaal moet aan deze onderwijsaanbieders worden voorgelegd om vraag en aanbod op de arbeidsmarkt te verbeteren.
- Versterk de vraagzijde voor nucleaire geneeskunde. Door ervoor te zorgen dat nieuwe nucleair geneeskundige therapieën aan patiënten kunnen worden aangeboden, wordt het maatschappelijke verdienvermogen vergroot (betere gezondheidszorg) en ook het economische verdienvermogen (als er Nederlandse bedrijven bij betrokken zijn). Daarvoor zijn echter investeringen nodig in ziekenhuisinfrastructuur en -faciliteiten.

FAST moet faciliteren dat de voorgestelde aanbevelingen door de belanghebbende in het ecosysteem worden opgepakt, bijvoorbeeld in het voorstel van het DECISIVE-consortium en in de raodmap van de kwartiermaker medisch isotopen.

1 Introduction

1.1 Context and motivation for this study

Nuclear medicine has seen many new developments in the past few years that have changed the field. Traditionally, nuclear medicine was primarily involved in diagnostics, with only few therapeutic applications. Developments in new radiopharmaceuticals have led to a shift towards therapy, which increased the role of nuclear medicine in the therapy of patients – so far mainly in the fields of oncology and urology. Experts expect that the use of radiopharmaceuticals will increase in the coming years and that nuclear medicine will be more involved in therapy, next to its use in diagnostics.

Currently, the Netherlands has a strong position in the production of medical radioisotopes with the existing HFR reactor operated by NRG. The HFR is however reaching its end of life. In 2023, the Dutch government therefore decided to invest in PALLAS, a new research reactor to produce medical radioisotopes. In addition, SHINE is preparing for its European production of medical radioisotopes in the Netherlands as well. At the same time, Novartis is also planning to expand its existing production facilities for radiopharmaceuticals in the Netherlands. In addition, recently the FIELD-LAB was opened in Petten – a collaboration between industry and several academic hospitals to support drug development in nuclear medicine.

These developments provide a good foundation to make the Netherlands a hotspot for nuclear medicine in Europe. To reap the full benefits for the Netherlands and Dutch patients, it is important that these initiatives are embedded in a wider, national innovation ecosystem for nuclear medicine.

This study was requested by the Centre for Future Affordable Sustainable Therapies Development (FAST) to provide more insight into the current innovation ecosystem for nuclear medicine and recommendations to improve the ecosystem in the Netherlands. The study should inform the activities of FAST in nuclear medicine, the nuclear medicine community and specifically the 'quartermaster' for medical isotopes who has been appointed by the Dutch Ministry of Health, Welfare and Sport (VWS) to bring together actors in nuclear medicine to develop a plan to further develop R&D in nuclear medicine in the Netherlands. In addition, the report should inform DECISIVE, a consortium of actors in the Dutch innovation ecosystem for nuclear medicine that aims "to improve and accelerate innovation and business activities in nuclear medicine"[1]. To that end, they are preparing an application for the Dutch National Growth Fund.

This study investigates opportunities to improve the earning capacity for the Netherlands and opportunities to strengthen the innovativeness of the Dutch innovation ecosystem for nuclear medicine. This should contribute to an innovation ecosystem in which radiopharmaceuticals are efficiently developed, making them available faster to patients against an acceptable price.

1 See: https://www.ngfdecisive.nl/

1.2 Key definitions, scope, and concepts

In the context of this study, we consider **innovations in nuclear medicine** to be new radiopharmaceuticals, medical radioisotopes, or related technology. The focus of this study is on radiopharmaceuticals (i.e. nuclear medicines), be it for diagnostic or therapeutic use. Medical devices used in nuclear medicine and radiology are not in scope of this study. The focus is primarily on the Netherlands innovation ecosystem, but we will also describe the EU innovation ecosystem for nuclear medicine and in lesser detail the innovation ecosystem for nuclear medicine in the USA.

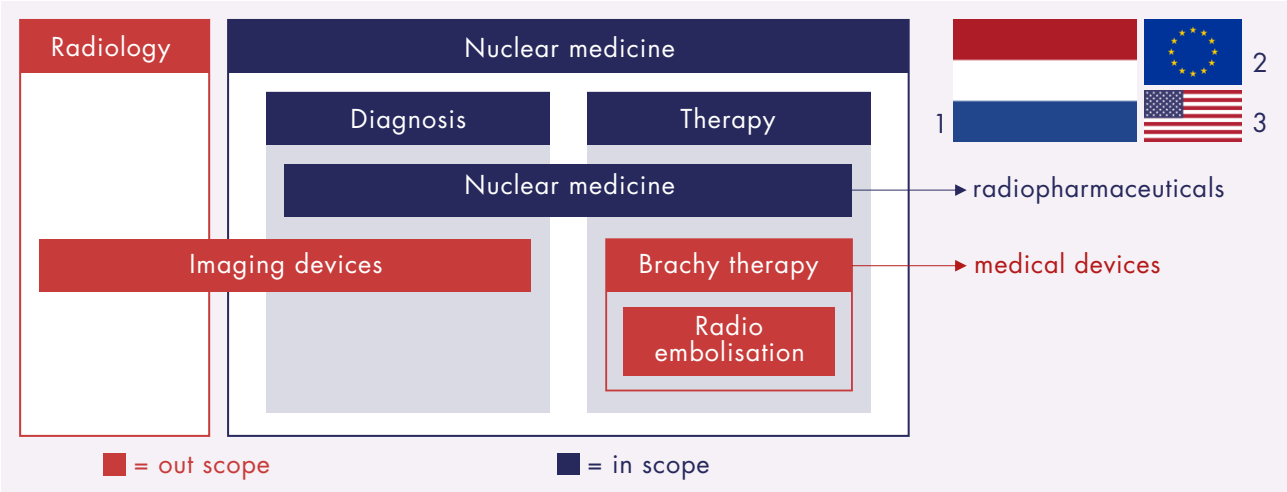

Figure 1 Scope of this study

An **innovation ecosystem** constitutes a set of actors, activities, facilities (infrastructure), financing and rules in which innovations in nuclear medicine are created. Other important aspects of such an ecosystem are its culture (e.g. cooperation, trust, risk-taking, competition and openness), scale (having a critical mass) and international connectiveness.

Innovativeness[2] is the ability of an innovation ecosystem to develop innovations in nuclear medicine and bring those on the market, i.e. to the patient.

Earning capacity[3] is the ability of an innovation ecosystem to generate sustainable economic and societal growth. Sustainable economic growth means a long-term effect on the GDP of the Netherlands, which can be realised by an increase in economic activity (such as more products or services sold), more business, more jobs, more export, or a higher productivity (which does relate to a better health of the working population). Sustainable societal growth means a long-term effect on better (health) care for patients through the faster availability of new high-quality treatments at an acceptable price.

2 In Dutch: innovatiekracht.
3 In Dutch: verdienvermogen.

Increasing earning capacity requires to invest in the development of radiopharmaceuticals and medical radioisotopes, and to get return on investment by earning/benefiting from the production of these radiopharmaceuticals and medical isotopes across the value chain. At the same time earning capacity should be in balance with the societal costs and benefits of nuclear medicine (high prices for radiopharmaceuticals may increase the earning capacity, but also increase the societal costs and the availability of these medicines to patients).

1.3 Background: nuclear medicine

Nuclear medicine is a branch of medicine that serves as the basis of various diagnostic (mostly) and therapeutic procedures. It involves the use of radioactive substances (nuclear medicines, i.e. radiopharmaceuticals) in the diagnosis (imaging) and therapy (treatment) of diseases such as certain types of cancer, neurological and cardiovascular diseases. Unlike in radiology, in nuclear medicine radiation is emitted from within the body rather than transmitted through the body from an external source such as with X-rays imaging[4].

Nuclear medicines or radiopharmaceuticals consist of radioisotopes, its radioactive component, combined with pharmaceutical compounds. Radiopharmaceuticals are taken internally (orally or intravenously) and can emit various types of radiation, including gamma rays, beta particles, or alpha particles, depending on the used radioisotope. Commonly used radioisotopes in radiopharmaceuticals include technetium-99m (^{99}mTc), fluorine-18 (^{18}F), iodine-131(^{131}I), lutetium-177 (^{177}Lu), and yttrium-90 (^{90}Y)[5]. The radiopharmaceutical is distributed in the body, often targeting specific cells, and the radiation of the isotope is captured by an external detector to form images. This process is referred to as nuclear imaging, and enables physicians to assess organ function, detect abnormalities and evaluate the effectiveness of treatments. For instance, nuclear imaging can be used in oncology to observe abnormalities, growths, or tumours. This helps oncologists accurately diagnose the presence and extent of cancerous lesions, guiding treatment decisions.

Nuclear medicine therapy is limited but increasingly being used to treat various diseases, particularly cancer[6]. When administered internally, the radiopharmaceutical accumulates in the target tissue or organ, killing the abnormal cells with radiation. During therapy, extra care is taken to avoid damage to healthy parts of the body. This is done by calculating a low radiation dose (dosimetry) for sufficient treatment. Radiation therapy can also be applied through 'external beams' by a radiotherapist. A treatment that uses high-energy radiation beams to target and destroy cancer cells. The latter is however outside the scope of this report.

Nuclear medicine physicians play a crucial role in the multidisciplinary team of healthcare practitioners (HCPs), collaborating with specialists from various fields such as oncology, cardiology, and urology. In a nuclear medicine department, specialised equipment (such

4 R, D, Badawi. (2014). Nuclear Medicine. Physics Education, 36(6), 452.
5 Technopolis Group (2021). Study on sustainable and resilient supply of medical radioisotopes in the EU: Therapeutic Radionuclides
6 Technopolis Group (2021). Study on sustainable and resilient supply of medical radioisotopes in the EU: Therapeutic Radionuclides. JRC.

as PET or SPECT scanners) is used for imaging procedures to diagnose a wide range of conditions. Nuclear medicine physicians are specially trained to oversee the administration of radiopharmaceuticals. Unlike departments such as oncology or cardiology that focus on specific diseases or specialties, nuclear medicine departments combine a range of specialties. They work in tandem with other departments to ensure comprehensive patient care. These departments rely on the nuclear medicine department for effective disease diagnosis and management.

Nuclear medicine is undergoing a significant transformation in various areas of patient care applications (innovative radiopharmaceuticals, hardware, software). The past decade has seen significant growth of nuclear medicine. The combined use of a single pharmaceutical with the same or a different radionuclide[7] in both diagnosis and therapy, 'theranostics', is expected to become an important tool for medicine in the future.[8] The roles within hospitals are evolving, as nuclear physicians are taking on greater responsibility and influence in patient care and treatment[9]. This shift is accompanied by changes in the education and training of nuclear medicine professionals, focusing on integrated care and treatment methods. Consequently, nuclear medicine physicians are more involved in direct patient care, including planning and implementing treatment strategies using radiopharmaceuticals. Currently, the European Union (EU) is making significant strides in nuclear medicine applications in personalised care and targeted diagnosis in radiopharmaceuticals[10]. Moreover, the European Association of Nuclear Medicine (EANM) has laid down a framework to advance high-quality nuclear medicine services. This framework aims to enhance standards, value, quality, access and outcomes of nuclear medicine therapies and dosimetry in clinical practice. This reflects a broader trend in healthcare towards a multifaceted approach, integrating strategies across hospital departments to personalise patient care[11].

7 For example: 68Ga-DOTATOC to target neuroendocrine tumours (specifically the somatostatin receptors on their cell membranes) in PET diagnosis followed by a therapy using 177Lu-DOTATOC or 90Y-DOTATOC to target and kill the neuroendocrine tumours. See: https://uihc.org/health-topics/what-theranostics.

8 J. Urbain et al. (2023). Theranostic Radiopharmaceuticals: A Universal Challenging Educational Paradigm in Nuclear Medicine, Journal of Nuclear Medicine.

9 ABNM, D. M. A. The Changing Landscape of Nuclear Medicine and a New Era. The" NEW (Nu) CLEAR Medicine". A Framework for the Future. Frontiers in Nuclear Medicine, 3, 1213714.

10 Statement of the European Association of Nuclear Medicine (EANM) for a better inclusion of the particularities of Radiopharmaceuticals within the Review of Directive 2001/83EC on Pharmaceutical Legislation, (2021). EANM. Available at: https://www.eanm.org/content-eanm/uploads/2021/12/EANM_Radiopharmaceuticals-Directive-2001-83_Final.pdf

11 EANM Position Paper Nuclear Medicine. What it is. Where it goes. What it needs. Available at: https://www.eanm.org/content-eanm/uploads/2022/07/EANM- overarching-narrative_0707.pdf

1.4 Reading guide

In the next chapter of this report (Chapter 2), we will first introduce the process for the development of radiopharmaceuticals from idea to clinical use in the Netherlands. Information on each stage is provided. For each stage we provide information experienced barriers in the Netherlands.

In Chapter 3, we provide an overview of the Dutch innovation ecosystem, introducing its actors and key characteristics. We also provide the strengths and weakness of the current ecosystem and its opportunities and threats for the future.

In Chapter 4 we place the Dutch ecosystem in an international perspective by sketching first the innovation ecosystems for nuclear medicine at EU level and in the USA. We also position the Netherlands in a wider set of countries, including the USA, and draw lessons for the Dutch ecosystem.

In Chapter 5 we draw conclusions on the Dutch innovation ecosystem and innovation process in nuclear medicine and provide recommendations to strengthen the innovativeness of the ecosystem and its earning capacity.

In the annexes we provide an overview of regulatory frameworks in the Netherlands, EU and USA that apply to nuclear medicine and the development of radiopharmaceuticals, a list of identified actors in the Dutch innovation ecosystem for nuclear medicine, and a methodological overview.

2 The development of radiopharmaceuticals

2.1 Overview of the development process/value chain for radiopharmaceuticals

The process from research and development (R&D) of radiopharmaceuticals to their use by patients and physicians encompasses several key steps. These steps are outlined in Figure 1. The following sections provided information on what each stage entails.

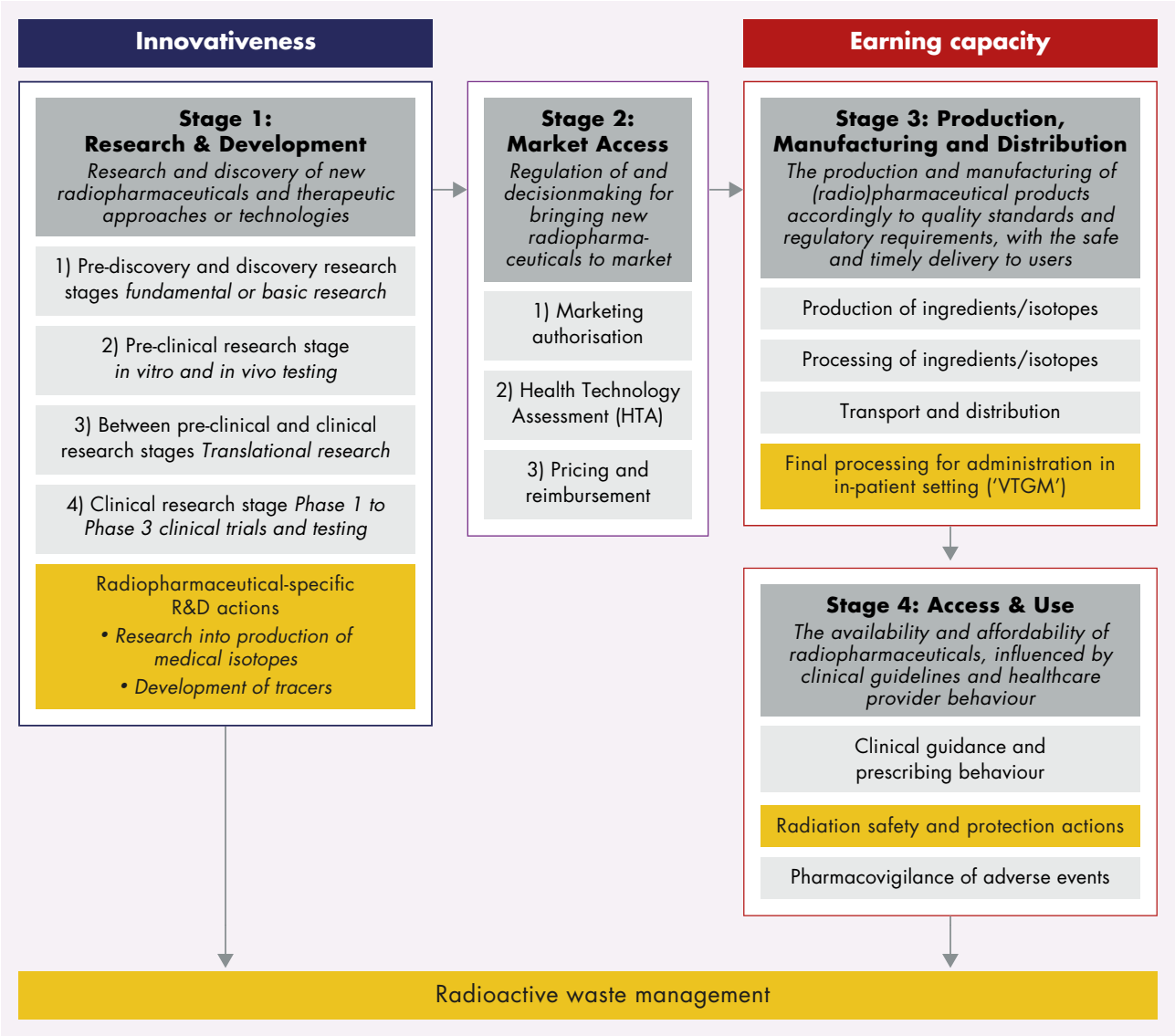

Figure 2 Schematic overview of the development process for radiopharmaceuticals

Notes: Steps or actions marked by a yellow box are specific to nuclear medicine; those marked by a grey box are general for all pharmaceutical products, including radiopharmaceuticals. VTGM = "Voor Toediening Gereed Maken" = prepare for administration.

2.1.1 Stage 1: Research & development

Research starts with **pre-discovery and discovery** stages. This process is also referred to as fundamental research or 'basic research', defined as 'experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundation of phenomena and observable facts, without any particular application or use in view.'[12] During pre-discovery, researchers may focus on understanding disease mechanisms and potential targets or pathways for addressing these mechanisms, while discovery focuses on using this information on diseases or new technologies to search for new or existing molecular compounds which can address these.[13],[14] This stage encompasses various aspects, such as the identification of radioisotopes, chemical and radiochemical analysis to study and balance radioactive elements within the radioisotope and subsequently, nuclear pharmacy, involving the formulation of dosages that are designed to establish effective and safe administration. However, the primary focus of this stage is to identify the most effective radioisotopes or radiopharmaceuticals: various isotopes may be identified and undergo testing to evaluate their medical efficacy and considering the biological effects, possible harm, or side effects.[15],[16]

Once a promising compound is identified through these preliminary stages of research, the compound will proceed to **pre-clinical research** where in vitro and in vivo tests[17] are conducted to test for toxicity, efficacy, and the mode of action or formulation.[18],[19] The preclinical stage assesses the biological effects of the radioisotope by observing biopathology and radiobiology.[20] In the context of radiopharmaceuticals specifically, preclinical research involves the selection of a suitable radionuclide through the process of in vitro characterisation to establish how the radiopharmaceutical[21] binds with the appropriate cells (such as a malignant tumour cell). This stage is crucial for researchers as it aids in understanding which receptor and types of tumours the radiopeptide can potentially target.[22]

A **translational research** stage then facilitates the application of the basic scientific discoveries to clinical settings by bringing together different disciplines for feedback.[23] This stage acts as

12 Eurostat (2021). Glossary: Basic Research. Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Glossary:Basic_research
13 Singh et al., (2023). Drug discovery and development: introduction to the general public and patient groups. Front. Drug Discov. Vol. 3. 2023. https://doi.org/10.3389/fddsv.2023.1201419.
14 U.S. Food & Drug Administration (2018). Step 1: Discovery and Development. FDA.gov. Available at: https://www.fda.gov/patients/drug-development-process/step-1-discovery-and-development
15 Based on roundtable discussions.
16 Based on interview data.
17 In vitro refers to studies performed outside of a living organism, while in vivo refers to studies performed inside of a living organism (e.g. animals).
18 Singh et al., (2023). Drug discovery and development: introduction to the general public and patient groups. Front. Drug Discov. Vol. 3. 2023. https://doi.org/10.3389/fddsv.2023.1201419
19 U.S. Food & Drug Administration (2018). Step 2: Preclinical research. FDA.gov. Available at: https://www.fda.gov/patients/drug-development-process/step-2-preclinical-research
20 Based on interview data.
21 A compound that combines a stable peptide, (a short amino acid) coupled with a radionuclide, an unstable nucleus or atom that undergoes radioactive decay emitting radiation. The peptide component provides the targeting specificity, often used for targeted therapy.
22 Knapp, F. F., & Dash, A. (2016). Radiopharmaceuticals for therapy. New Delhi, India: Springer.
23 Mahalmani et al., (2022. Translational research: Bridging the gap between preclinical and clinical research. Indian Journal of Pharmacology, 54(6),393.

an interface between basic science and later clinical application of discovered compounds, seeking to ensure the compound makes it into therapeutic development.[24] It is a diffuse stage that encompasses elements of pre-clinical research and clinical trials, as in each step from science some translation towards the clinical use occurs (first to humans, then to patient and then to practice). Translational research can include various studies and developments required to get approval for clinical trials, such as optimisation studies, proof-of-concepts and development of processes and protocols for clinical trials, and generating additional (in-vivo or in-vitro) evidence.

Once these steps have all been completed, and the compound in question is deemed safe and efficacious, the product can move to **clinical trials** in humans. There are four types of clinical trials[25]:

1. **Phase I**: testing of new medicines in a small group of patients to evaluate dosage ranges and safety.
2. **Phase II**: testing of medicines found safe in Phase I in a larger group to assess efficacy and monitor adverse events.
3. **Phase III**: testing of medicines in larger populations across regions/countries to assess efficacy and monitoring of adverse effects, and the final clinical test required for country approval.
4. **Phase IV**: post-authorisation testing of medicines (see Stage 2 below), if need for further testing of risks and benefits and to monitor effectiveness in real-world use.

For radiopharmaceuticals, clinical trials vary, based on the type of radiopharmaceutical and targeted disease and, as radiopharmaceuticals are designed to target specific pathways or receptors, trial designs need to be tailored to these specificities. For example, radiopharmaceuticals targeting a receptor expressed on a cancer cell should undergo a specific study(s) to evaluate binding affinity and internalisation into the tumour. The complexity of the disease in question will also influence how extensive the clinical process is and may require more safety assessments due to the sensitivity of the nervous system.[26]

For all clinical trials the radiopharmaceutical needs to be produced according to Good Manufacturing Practices (GMP, see 2.1.3 for more detail). This sets legal requirements and high standards on the production process and facilities for radiopharmaceuticals, also for small batches used in clinical trials.

2.1.2 Stage 2: Market access

If a new product is successful in clinical trials, the pharmaceutical or biotechnology company (or in some instances other types of research organisations) with the rights to the compound or product will seek to bring it to market. To do so, they must obtain **marketing authorisation** from a relevant regulatory agency. This step is required in any country. Within the EU

24 Butler D. (2008). Translational research: crossing the valley of death. Nature, 453:840–2.
25 World Health Organisation (2024). Clinical trials. WHO.int.
Available at: https://www.who.int/health-topics/clinical-trials#tab=tab_1
26 Vermeulen, K., Vandamme, M., Bormans, G., & Cleeren, F. (2019). Design and challenges of radiopharmaceuticals. In Seminars in nuclear medicine (Vol. 49, No. 5, pp. 339-356). WB Saunders.

this procedure is outlined in the European Union Directive 2001/83/EC. This function is performed by the European Medicines Agency (EMA) for new pharmaceutical products in the EU. Marketing authorisation is required for in the EU for industrially prepared radiopharmaceuticals as well as radionuclide generators, radionuclide kits, and radionuclide precursor radiopharmaceuticals. Radiopharmaceuticals prepared from already authorised components do not require marketing authorisation. The EMA will review findings from clinical trials, as well as other evidence or information provided by the applicant, to assess the safety, efficacy, and quality of the product in question. If the EMA grants a marketing authorisation, the product is eligible to be brought on the market in all EU Member States. Depending on factors in each Member State, access to the product may be immediate, or subject to delaying factors.

Once a product receives marketing authorisation in the EU, it undergoes a **health technology assessment (HTA) at national, Member State level**. This process, which differs per Member State, is a systematic assessment evaluating the properties and direct and indirect effects of the product in question, covering medical, economic, social and ethical issues, with an aim of informing decision-making and resource allocation.[27] The findings and recommendations resulting from HTA are used for **pricing and reimbursement decisions**: a question of whether the public healthcare system will cover the product in question, and at what financial cost.

The availability of radiopharmaceuticals will ultimately be dependent on, at least in part, commercial decisions around the (potential for) return on investments made during R&D and production. These decisions may be influenced by relatively small markets and patient populations for radiopharmaceuticals.[28] Novel funding mechanisms may be used to ensure risk and responsibility is balanced between the healthcare system and the marketing authorisation holder.

2.1.3 Stage 3: Production, manufacturing, and distribution

Production of ingredient/isotopes: To produce radiopharmaceuticals, medical radioisotopes are needed as active pharmaceutical ingredient. Medical radioisotopes are generally produced through nuclear reactions which occur when a source material is bombarded with elementary particles, such as neutrons, protons, or electrons. The source material (originally extracted from mined minerals or ores) is often a stable isotope, which can be naturally occurring or is isotopically enriched.[29]

In a nuclear reactor, or in accelerator-based neutron sources such as SHINE deploys, these target materials are bombarded with neutrons to create medical radioisotopes. In cyclotrons (or other types of charged particle accelerators) the targets are bombarded with electrons or protons. The latter results in proton rich isotopes, generally with a short half-life time, that are mainly used for diagnostic purposes (such as PET), but also some therapeutic applications

27 European Commission (n.d.). Health Technology Assessment: Overview. Health.ec.europa.eu. Available at: https://health.ec.europa.eu/health-technology-assessment/overview_en
28 Knapp, F. F., & Dash, A. (2016). Radiopharmaceuticals for therapy (pp. 3-23). New Delhi, India: Springer.
29 Technopolis Group (2023). Analyse waardeketens en grondstoffen voor medische isotopen. The Hague: Ministry of Economic Affairs and Climate.

exist.[30] Isotopes produced in reactors result in neutron rich isotopes, which can have longer half-life times, resulting in a wider palette of medical radioisotopes that can be used for therapeutic purposes.[31] Some key diagnostic medical radioisotopes are also produced with nuclear reactors. Other neutron sources, for example SHINE, can also produce various neutron rich isotopes.

Processing of active ingredients/isotopes: Once the medical radioisotope is produced, it is extracted from the target material and either incorporated into a biochemical compound (aqueous solution with ketone, amine, or other organic solvents) in a generator directly or directly prepared as a radiopharmaceutical. The medical radioisotopes are often linked to a tracer molecule that targets specific (e.g. cancer) cells. Rigorous quality control measures are implemented to ensure the safety, purity, and efficacy of the radiopharmaceutical.

Transport and distribution: Due to the short shelf life of some isotopes, particularly those used in positron emission tomography (PET), timely transport is critical to ensure that the radiopharmaceutical is still effective upon arrival. Radioisotopes that can be distributed in generators (from which the medical radioisotope can be eluted for labelling in hospitals) are mostly transported via ship and fewer by air and truck (in smaller quantities) with a measurable external radiation field.[32]

Final processing in in-patient setting: A radiopharmaceutical is prepared for patient administration in a hospital setting. A radiopharmacy unit (staffed by radiopharmacists or nuclear pharmacists) will receive the medical isotopes or radiopharmaceuticals and prepare them for clinical use and patient administration. Specific aspects in preparation are considered to ensure quality and safety of distribution. These include dosage, patient characteristics, biological interactions, and side effects (of the absorbed radiation) and specific medical procedures are considered[33].

Good Manufacturing Practices (GMP) requirements set out standards to ensure the manufacture and production are consistent and meet the quality required by the marketing authorisation for the product.[34],[35] Aspects of GMP include quality control, ensuring high quality and standards, ensuring the product is appropriate for its intended use, and assessing whether the radiopharmaceuticals meet the requirements of the clinical trial or marketing authorisation[36]. The reproducibility of the process is key in ensuring quality, efficacy, and safety standards across different batches.[37]

30 Technopolis Group (2023). Analyse waardeketens en grondstoffen voor medische isotopen. The Hague: Ministry of Economic Affairs and Climate.
31 NucAdvisor (2021). Co-ordinated Approach to the Development and Supply of Radionuclides in the EU. Brussel: European Commission.
32 The transport of radiopharmaceuticals in the United States, U.S. Department of Energy Office of Scientific and Technical Information, (2004). https://www.osti.gov/etdeweb/biblio/20773285
33 Owunwanne, A., (1994). The Handbook of Radiopharmaceuticals.
34 Knapp and Dash (2016). Radiopharmaceuticals for therapy (pp. 3-23). New Delhi, India: Springer.
35 Ekinci, M., Santos-Oliveira, R., & Derya, İ. Ö. (2022). Quality Assurance and Quality Control of Radiopharmaceuticals: An Overview. Journal of Faculty of Pharmacy of Ankara University, 46(3), 1044-1063.
36 European Medicines Agency (n.d.). Good Manufacturing Practice. EMA.europa.eu. Available at: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/compliance-research-and-development/good-manufacturing-practice
37 Knapp and Dash (2016). Radiopharmaceuticals for therapy (pp. 3-23). New Delhi, India: Springer.

2.1.4 Stage 4: Access and use

Once a product has received marketing authorisation and a positive HTA recommendation, a pricing and reimbursement decisions will be made. In the Netherlands, if this decision is positive the product is available to the patient as reimbursed care. Depending on the healthcare system in EU Member States, uptake may be affected by pharmaceutical budgets and/or insurance covers, or, depending on the product, patient co-payments. In addition, uptake of the product may also be influenced by:

- Clinical guidelines: most healthcare systems in the EU will use clinical guidelines for healthcare providers to standardise care, often set by medical associations or expert groups. However, the speed with which these guidelines are updated (and what line of care the product is recommended for use at), and whether adherence to guidelines is mandatory, can affect uptake.
- Prescribing behaviours: if guidelines are not updated with frequency, or are not mandatory, uptake of medicines can be dictated by healthcare provider behaviours or their knowledge of (or training in) new treatment options.

Once a product is in use, there are stringent pharmacovigilance processes (including phase IV clinical studies) in place. While clinical trials show a certain amount of efficacy under controlled circumstances, pharmacovigilance monitors whether medicines are safe throughout use once available on the market. Safe use within a hospital setting will also be overseen by inspections and European or national guidelines/standards. This includes ensuring staff are trained in radiopharmaceutical-specific safety steps, such as aseptic and processing practices to avoid contamination when using kit-based radiopharmaceuticals (which are subject to microbiological contamination if not used correctly).[38] Patient organisations may also monitor patient experience around new treatment options.

2.1.5 Other: Decommissioning and waste processing

The Basic Safety Standards (BSS) set by the International Atomic Energy Agency (IAEA)[39] outline the importance of decommissioning and disposal of radioactive waste throughout the value chain or lifecycle from R&D, to use to prevent environmental contamination and reduce the potential of health hazards.[40],[41] This involves minimising the risk of radiation exposure to both workers and the public. Decommissioning and waste processing are also covered by regulatory, production and manufacturing requirements for radiopharmaceuticals.

Radioactive waste is generated throughout all stages of nuclear medicine development, production, and use. Radioactive waste is also excreted by patients in various therapies and requires facilities and precautions to safely deal with this waste and radiation in hospitals. This requires personnel that is trained in radiation protection and special facilities to safely contain and deal with the radioactive waste from patients. In the Netherlands, this waste must

38 Vermeulen, K., Vandamme, M., Bormans, G., & Cleeren, F. (2019, September). Design and challenges of radiopharmaceuticals. In Seminars in nuclear medicine (Vol. 49, No. 5, pp. 339-356). WB Saunders.

39 International Atomic Energy Agency, Basic safety standards series, Application of the concepts of exclusion, exemption and clearance, Safety Guide (2004). Source: https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1202_web.pdf

40 Ojovan, M. I., & Steinmetz, H. J. (2022). Approaches to Disposal of Nuclear Waste. Energies, 15(20), 7804.

41 Kanagamani, K., Geethamani, P., & Narmatha, M. (2020). Hazardous waste management. In Environmental Issues and Sustainable Development. IntechOpen.

be disposed to the Dutch radioactive waste management organisation COVRA, which safely collects, processes, and stores all radioactive waste in the Netherlands.

2.2 Barriers for the development of radiopharmaceuticals in the Netherlands

The nuclear medicine industry in the Netherlands faces multifaceted challenges, hindering its growth and innovation. Through interviews and consultation with stakeholders involved in the nuclear medicine industry, the following challenges have been identified as barriers for the development of nuclear medicine and systematically grouped according to each stage within the development process. They include barriers in Stage 1 (Research and Development), Stage 2 (Market Access), Stage 3 (Production, Manufacturing and Distribution), and Stage 4 (Access and Use). Each category highlights core challenges, offering insights into understanding the specific challenges encountered throughout the value chain.

2.2.1 Stage 1: Research and Development

The R&D is a heavy-laden stage in the value chain. It is critical in identifying isotopes and radiopharmaceuticals, and generating evidence for clinical application.

Findings from surveys and interviews indicated that there is a **fragmented approach in the R&D stage**. Various responses and interactions confirm that research is not coordinated between institutions or research groups and collaboration is rather limited. This results in various smaller studies that are less well-placed to scale-up and in limited knowledge sharing between Dutch ecosystem actors involved in R&D.

In addition to maintaining **security of supply of materials** and radioisotopes (*see section 2.2.3*), **suitable facilities** such as hot labs, processing facilities, GMP labs and infrastructure at hospitals (such as for waste collection, shielded rest rooms etc.) are needed to conduct R&D in nuclear medicine. Only a few organisations in the Netherlands have these facilities for R&D including clinical studies in nuclear medicine[42],[43]. The Netherlands also has limited facilities for large-scale clinical studies for nuclear medicine, there has been however, recent investment into enhancing this infrastructure[44],[45],[46]. Few academic hospitals have the required facilities to both produce and prepare radiopharmaceuticals that can be used in clinical studies. Due to short half-life times of cyclotron-produced medical radioisotopes, this may affect the number of

42 Roelofs, F., Breijder, P., Hania, R., de With, G., de Haas, G. J., van den Broek, J., & Schram, R. (2024). Highlights and outlook of the Dutch PIONEER 2021–2024 R&D program. Nuclear Engineering and Design, 417, 112873.

43 RIVM, (2020). Supply security for medical radionuclides- additions 2020. Available at: https://www.rivm.nl/bibliotheek/rapporten/2020-0171.pdf

44 PALLAS (2023). Opening of new facility in Petten accelerates development of cancer treatments. Available at: https://www.pallasreactor.com/en/news/https-www-pallasreactor-com-en-news-opening-of-new-facility-in-petten-accelerates-development-of-cancer-treatments

45 NRG (2015). Research & Innovation Activities, NEA International Workshop on 'Nuclear Innovation Roadmap' (NI2050) – Netherlands. Available at: https://www.oecd-nea.org/ndd/workshops/ni2050/presentations/docs/2_12_Pays_Bas_Netherlands_NRG_Research%20and%20Innovation%20Activities%20by%20F_Roelofs.pdf

46 Scholten, C., Petrosova, L., van de Veen, G. (2022). Medical isotope production using local cyclotrons: A comparative study between Denmark and the Netherlands. Technopolis Group. Available at: https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/rapporten/2022/01/31/productie-van-medische-isotopen-met-cyclotrons/Technopolis+Group+Medical+isotope+production+using+local+cyclotrons+2022.pdf

hospitals (and thus patients) that can be included in clinical studies/trials or can benefit from these medicines[47].

From stakeholder interactions, **delays in obtaining permits** for different stages of nuclear medicine development and implementation were also highlighted as an obstacle. Permits for research studies necessitate approval from a medical ethical committee, a process that is said to take more time in the Netherlands than in some other European countries according to interviewees. Permits pertaining to nuclear facilities, regulated by the ANVS, are perceived as long and have had delays. These delays contribute to longer timelines for the development of nuclear medicine in the Netherlands compared to faster pathways available in other countries such as the U.S.

Funding for investigator-led clinical research in nuclear medicine is said to be difficult to obtain in the Netherlands. There are few and no specific programmes for funding such research (especially not consistently along different stages).[48] Acquiring funding for conducting investigator-led clinical trials is challenging. For smaller R&D actors this is especially challenging for the more expensive phase III trials. Interviews underscored that the **costs to develop new medical radioisotopes** are high and are often difficult to finance in nuclear medicine research projects. Investors can cover these costs, but such investments are often better available for the later stages of R&D due to lower risks. Investing in pharmaceuticals in general is associated with high risks, as the majority of pharmaceuticals developed will not make it to the market. This risk of failure reduces with each successful clinical trial stage. The availability of investor funding depends on the potential patient population and the expected (global) willingness to pay for the medicine (which also depends on reimbursement).[49] Start-ups in nuclear medicine face challenges in attracting investments.

The interviews also indicated that relevant **regulation for clinical trials in the Netherlands appears to be stricter** than required by EU Directives and, with that, than other European Member States transposing Directives in a less stringent fashion. Specific areas of concern include additional national rules in clinical research and trials compared to the EU framework and perceived increasing regulation for clinical trials. This is related to the implementation of EU regulation, where the decentralised supervision of medical ethical committees in the Netherlands make investigator-led early clinical research more complicated than in several other EU countries.[50]

47 Killbourn, M. R., et al. (2020). Production of Short Half-Life PET Radionuclides. Handbook of Radiopharmaceuticals: Methodology and Applications, 45-69.

48 In addition to insights provided by consulted stakeholders, we have not found such programmes at ZonMW and NWO. Some funding may be available through the Topsector Life Sciences and Health (Health ~ Holland), but requires public-private collaboration. Funding from non-profit organisations is available for this kind of research, for instance for oncology through KWF. This requires to define research from (in the example of KWF) oncological medical need and close collaboration with oncologists.

49 SiRM, L.E.K. Consulting & RAND Europe (2022). The financial ecosystem of pharmaceutical R&D: An evidence base to inform further dialogue.

50 J.C.F. van Oijen, I. Wallenburg, R. Bal, and K. J. Grit (2020). Institutional work to maintain, repair, and improve the regulatory regime: How actors respond to external challenges in the public supervision of ongoing clinical trials in the Netherlands. PLOS ONE 15(7): e0236545. https://doi.org/10.1371/journal.pone.0236545

Finally, Intellectual Property (IP) has been raised as a barrier in some interviews. These barriers are specifically with academia and SMEs. For academia and SMEs (such as start-ups) obtaining and maintaining **intellectual property rights** (IP) is expensive. A lack of financial resources to secure these rights is limiting them from competing effectively. As research required to bring a new nuclear medicine (i.e. radiopharmaceutical) to the market usually takes a long time, IP should be maintained for long period, resulting in additional costs. It is mentioned in various interactions that IP in academia is often not maintained long enough (beyond phase II clinical trials) for investors or for buy-out.

2.2.2 Stage 2: Market Access in the Netherlands

Interviewees noted that accessing the market for radiopharmaceuticals is challenging, although there was consensus that this difficulty is generally faced across the pharmaceutical industry. Bringing medicines to market takes time: the marketing authorisation approval crucial for **market entry may experience delays**, subsequent HTA and pricing and reimbursement processes are time-consuming (especially for expensive medicines), and may experience delays, gathering data for Health Technology Assessment (HTA) is difficult and time consuming. Consulted actors in the innovation ecosystem for nuclear medicine have attributed experienced delays in market entry to lack of personnel at authorities, slow procedures due to bureaucracy and unambiguous EU regulations for radiopharmaceuticals due to lack of protocols and limited experience with radiopharmaceuticals at marketing authorities.

Many consulted actors in the ecosystem for nuclear medicine address **strict regulation and procedures in the Netherlands for market access (HTA/reimbursement)**. This is however not specific for nuclear medicine and whether this is more restrictive than in other countries depends on the comparison. Indeed, in Germany various radiopharmaceuticals have been earlier accessible to patients than in the Netherlands. The Dutch system for market access is aimed at keeping costs for new medicines within boundaries. Expensive medicines will go through a more elaborate process before the medicine is reimbursed, requiring more detailed information on the effectiveness of the medicine compared to the standard (first line) treatment in the Netherlands. This can require specific Dutch (HTA) research, as international studies may have referenced a different first-line treatment. Such additional research may lead to further delays in the availability and reimbursement of new (nuclear) medicines in the Netherlands compared to other EU countries (such as Germany). Consequently, patients in the Netherlands may face delays in accessing these treatments, impacting their timely care – which is currently the case for Pluvicto®[51]. There is funding available to support evidence gathering on the (cost) effectiveness of a novel medicine compared to existing treatments in the Netherlands under the subsidy scheme *subsidieregeling veelbelovende zorg*[52]. This funding can support in the process of bringing novel, expensive medicines to Dutch patients under reimbursed care[53].

51 This medicine is currently in the 'sluis' awaiting completeness of the full dossier from the applicant since December 2022.
52 A grant scheme for promising care that is intended for relatively costly care that is proven to be effective.
53 Zorginstituutnederland.nl (n.d.). Veelbelovende zorg: subsidieregeling voor onderzoek naar potentieel veelbelovende zorg. Available at: https://www.zorginstituutnederland.nl/werkagenda/veelbelovende-zorg

The **Dutch market is relatively small** (in comparison to the nuclear medicine market in countries like the USA and Germany), leading to a lack of strong market presence. To address this, the Dutch industry primarily focuses on targeting the larger European market, where there is more demand.

2.2.3 Stage 3: Production, Manufacturing and Distribution

In this stage concerns have been raised about the **level playing field for businesses** in the production of medical radioisotopes. This is related to the full recovery of costs in prices for medical radioisotopes (which is an international discussion) when produced in facilities that are largely funded by the government. A level playing field makes it attractive for foreign businesses in the production of medical radioisotopes to locate in and do business from the Netherlands.

It emerged from stakeholder interviews that there is a **lack of key infrastructure**, such as radiopharmaceutical production facilities (hotcells/hot labs) that are designed to handle radioactive materials safely. This can be a bottleneck for further scale-up of production and innovation and for start-ups in the field of nuclear medicine to get access to such expensive, but required infrastructure.

From radioisotope realisation to production, the scarcity of critical starting materials, particularly finding the right stable isotopes, is a bottleneck to a continuous supply chain. This is exacerbated by a **dependence on resources** from other countries. Currently, the Netherlands depends on Russia for various (enriched) stable medical radioisotopes (mostly for therapeutic purposes). This creates a reliance on the availability of the medical radioisotopes that can be determined by the stability of the country's industry, political climate, and other factors.[54]

From the data collection during this study no bottlenecks in (domestic) distribution and hospital pharmacies have emerged.

2.2.4 Stage 4: Access and Use

The Netherlands currently faces **shortages in human capital** necessary to make the expected growth in nuclear medicine possible, both in industry and hospitals. The nature of the required workforce is multidisciplinary. Some interviewees emphasised that attracting individuals with a chemical background willing to work within the nuclear medicine industry is challenging. This could be attributed to the absence of specialised education in radiochemistry. In addition, concerns were voiced about the capacity at radiation protection studies, the strong focus on radiology in the training of nuclear medicine physicians (instead of on internal medicine) and the changing skills needs for nurses at nuclear medicine departments when radionuclide therapy becomes more frequent.

54 Technopolis (2023). Analyse waardeketens en grondstoffen voor medische isotopen. The Hague: Ministry of Economic Affairs.

The **absence of sufficient infrastructure** to accommodate and treat patients effectively with radiopharmaceuticals in some hospitals was also raised. The expected growth of the use of radiopharmaceuticals and the changing role of nuclear medicine physicians requires additional and specific infrastructure at hospitals to provide radiopharmaceutical therapy. Practical challenges include, just as for clinical trials, the lack of preparatory rest areas and specialised treatment rooms for patients undergoing nuclear medicine therapy. For protection measures, securing lead-shielded rooms for various therapeutic applications, such as prostate cancer, add further complexity. Such infrastructural needs, also limit the use of the imaging technology available, leading to less efficient use of expensive equipment and untapped potential for high-end treatment of patients. On a methodological level, the harmonisation of treatment protocols (incl. dosimetry) and developing specialised units with trained nurses is imperative for addressing these infrastructure barriers.

From the mini survey and interviews it emerged that **prescribing radiopharmaceuticals and integrating radiopharmaceuticals into clinical guidelines** can be an additional barrier to bring these medicines to patients. Clinical guidelines are set by professional societies that are organised per medical field. Nuclear medicine physicians are not always (well) represented in committees that develop guidelines for these medical fields. In addition, non-adherence to guidelines, lack of knowledge and lack of incentives, have been raised as barriers for transferring patients to the nuclear medicine department.

Lastly, there is an ongoing (political) **discussion about pharmacy preparation** (or: magistral preparation) of radiopharmaceuticals. For experimental radiopharmaceuticals, or medicines that are not on the market, pharmacy preparation is common practice. For most radiopharmaceuticals some pharmacy preparation for administration is always needed to tailor the dose to the patient or to prepare the medicine from e.g. a generator or label the cyclotron-produced medical radioisotope. However, some expensive radiopharmaceuticals that have received marketing authorisation but are not reimbursed in the Netherlands, are produced in-house by pharmacy preparation in some hospitals. These in-house produced medicines are reimbursed in the Netherlands.[55] This is considered by some as a temporary solution to provide expensive medicines to patients, but is also considered a risk for investments and the access to radiopharmaceuticals in the Netherlands in the long term. It reduces the level playing field for pharmaceutical businesses in the Netherlands and may affect the attractiveness of the Dutch innovation ecosystem for nuclear medicine negatively.

55 Ministry of Economic Affairs (2023). Achtergrondanalyse ten behoeve van besluitvorming over de PALLAS-reactor.

3 The Dutch innovation ecosystem for nuclear medicine

3.1 Actors in the innovation ecosystem

3.1.1 Overview

We have identified 120 actors that are active in the Dutch ecosystem for nuclear medicine spread across the Netherlands. The list of identified actors is provided in Appendix A. Although we cannot claim this list is complete, we believe it is quite extensive, as it was collected from various sources and reviewed by the studies advisory group. In the context of this study, it is used to see which actors are most prevalent in the ecosystem, as is depicted in Table 1.

Type	Amount
Departments of Nuclear Medicine in Hospitals [In brackets: academic hospitals (R&D)]	67 (7)
Equipment suppliers	15
Isotope producers	9
Pharmaceutical companies	8
Government organisations	7
Professional associations	5
Industry representation	3
Patient organisation	3
R&D in/for nuclear medicine (research (support) organisations apart from academic hospitals)	3
Total	**120**

Table 1 Identified actors in the Dutch ecosystem of nuclear medicine

In general, we see many hospitals with a department of nuclear medicine. Only five academic hospitals have GMP labs to produce and prepare radiopharmaceuticals in-house, four of which have their own cyclotron to produce medical isotopes. Only one non-academic hospital has such facilities. The innovation ecosystem has also quite some (commercial) suppliers, providing equipment for several aspects of nuclear medicine production and use (such as systems and equipment for handing nuclear materials, laboratory equipment for production and transportation). Furthermore, there are quite a number of producers of medical isotopes in the Netherlands, among others NRG (operating the current HFR and in the future PALLAS) in Petten, and soon SHINE in Veendam, and several cyclotron facilities located in or near hospitals.

Geographically, several clusters of actors in the innovation ecosystem for nuclear medicine can be identified (see Figure 3). Here various actors and facilities are in geographical proximity. Such locations can be termed hotspots within the Dutch ecosystem for nuclear medicine.

- **Amsterdam-Alkmaar-Petten region**: this cluster is characterised by many production facilities for radiopharmaceuticals, including a nuclear research reactor and various cyclotrons. It also contains various hospitals, including an academic hospital, and the Petten site with NRG-PALLAS and the FIELD-LAB.
- **The Hague-Delft-Leiden-Rotterdam region**: this cluster is characterised by a concentration of academic hospitals (Rotterdam and Leiden) and research organisations (academic hospitals and TU Delft), combined with various governments and authorities (incl. VWS and ANVS). In addition, the radiopharmacy department of GE Healthcare is also located in this region (Leiderdorp).
- **Utrecht region**: this cluster is characterised by the concentration of involved government authorities (such as RIVM, CBG and IGJ) and patient and professional organisations. The region has one academic hospital.

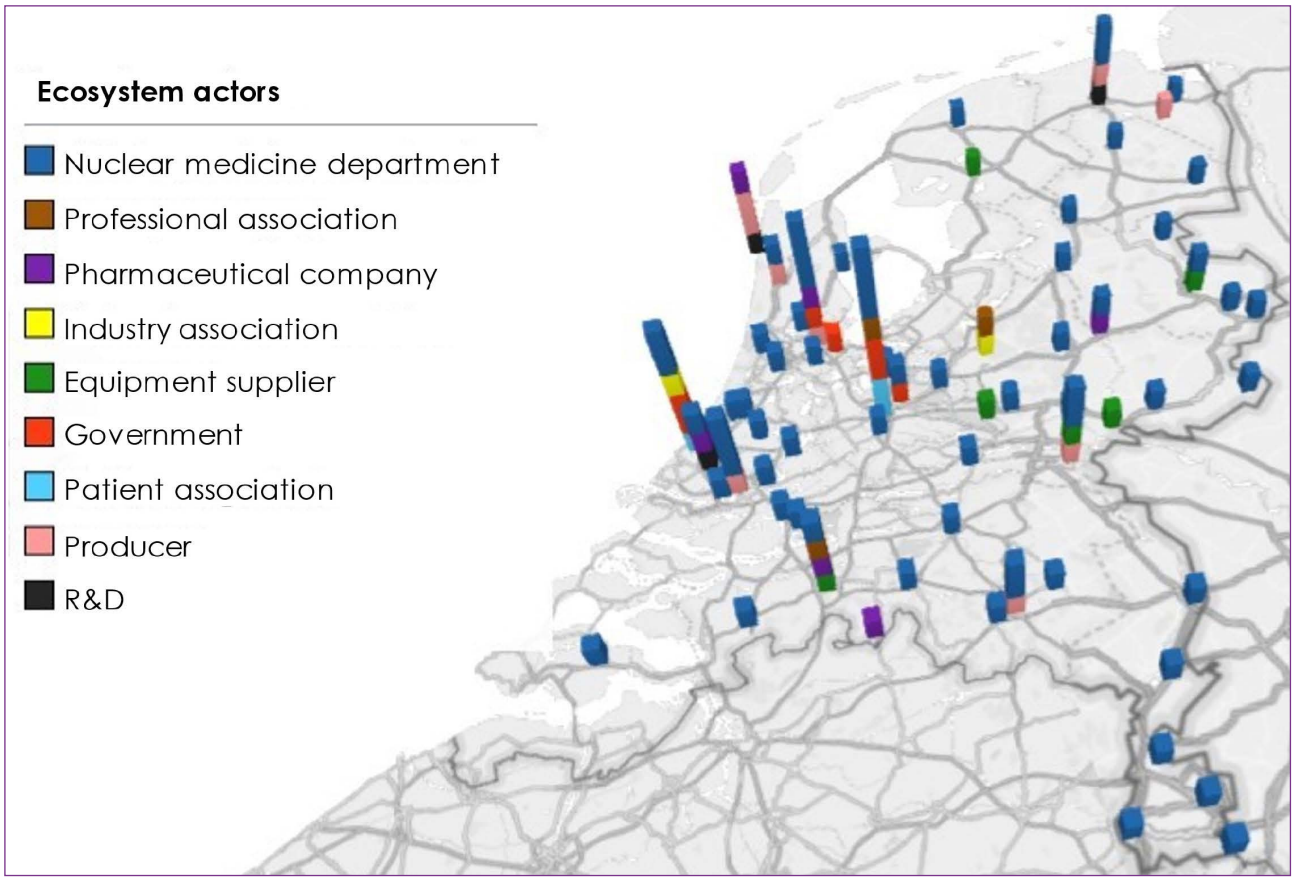

Figure 3 Schematic overview of the actors in the Dutch innovation ecosystem for nuclear medicine

- **Groningen-Veendam region**: this cluster has a medical cyclotron (UMCG), research cyclotron (KVI-RUG) and novel (still to be operational) production facilities for medical isotopes (SHINE). The region has one academic hospital (in Groningen).
- **Breda-Baarle Nassau region**: this cluster is characterised by pharmaceutical companies in nuclear medicine, the production site of Novartis/AAA/IDB Holland in Baarle-Nassau and the start-up TerThera in Breda, and hosts the office of the NVNG.
- **Nijmegen region**: this cluster has various equipment providers (Zereau and Von Gahlen), a cyclotron supplying medical radioisotopes and radiopharmaceuticals to other hospitals and for research (RTM), and an academic hospital (Radboudumc)

Figure 3 provides an overview of the locations of the identified actors in the innovation ecosystem for nuclear medicine.

The actors and their roles in the Dutch innovation ecosystem for nuclear medicine are discussed in following sections. In section 3.2, we will describe several key characteristics of this ecosystem.

3.1.2 Government and regulators

Key stakeholders within the Dutch national nuclear medicine ecosystem include the national government and regulatory bodies. Most regulations are formulated by the European Commission and approved by the European Parliament & European Council. This ensures uniformity in regulations across all member states. Nevertheless, the implementation and procedural aspects of these regulations vary from one country to another. Within the Netherlands, various organisations undertake the implementation of these regulations. Notably, a distinction is made between guidelines that specifically pertain to nuclear considerations and those concentrating on medical aspects.

3.1.2.1 Regulatory bodies addressing nuclear aspects and radiopharmaceuticals

When it comes to the nuclear aspect, the main regulatory body is the Authority for Nuclear Safety and Radiation Protection (ANVS). This organisation was founded in 2015 to centralise the government responsibilities and knowledge about the nuclear sector in a single authority. It falls under the jurisdiction of the Ministry of Infrastructure and Water Management[56] and aims to ensure that nuclear safety and radiation protection in the Netherlands meets the European standards. Companies or organisations that work with radiation require permits. The ANVS grants those permits, monitors compliance with the rules, and has the authority to take enforcement actions if necessary. The ANVS enforces international nuclear regulations and guidelines, and the Dutch Nuclear Energy Act. The Nuclear Energy Act is the basis for Dutch regulations in the field of nuclear safety and radiation protection, and as such also for the management of radioactive waste. The act consists of approximately 100 articles, which contain the principles for further regulation, licensing systems and governmental authorities.

56 Ministry of Infrastructure and Water Management (2021). National report for the Council Directive 2011/70/Euratom. Source: https://open.overheid.nl/repository/ronl-0ac91e23-f967-4cd9-95e9-abdf872bbf9c/1/pdf/bijlage-national-report-for-the-council-directive-2011-70-euratom.pdf

The Netherlands Labour Authority (NLA) monitors whether this Nuclear Energy Act is followed when it comes to worker protection[57]. Anyone working with (or being in proximity of) an X-ray machine or radioactive source is at risk of health damage, even at low doses. The NLA therefore monitors whether employers have properly organised workplaces to minimise the risks.

Lastly, there is attention from the government and regulatory bodies for nuclear medicine specifically as well. The National Institute for Public Health and the Environment (RIVM) has conducted studies on the production and use of radionuclides within the medical sector[58], focusing on supply security. RIVM also monitors the radiation exposure in the Netherlands and advises the government on topics regarding radiation protection. These studies concern effects on patients, workers, the population, and the environment.

The main ministry for nuclear medicine policy is VWS. The VWS programme for Medical Isotopes has the objective to ensure the supply security of medical isotopes and strengthen the nuclear knowledge infrastructure for the development of new (cancer) therapies. This includes addressing the issue of replacing the European production capacity, which largely consists of outdated research reactors. To achieve this, VWS can also provide funding, as it did for the PALLAS-reactor that will produce medical isotopes[59]. In 2023, the ministry of VWS appointed a 'quartermaster' to bring together actors in nuclear medicine to develop a plan to further develop R&D in nuclear medicine in the Netherlands.

3.1.2.2 Regulatory bodies addressing market access of medicines

Apart from regulatory bodies that address the nuclear aspects, there are also bodies that address the market access. The European Medical Agency (EMA) is the agency of the EU that is responsible for the marketing authorisation of medicines throughout the EU, including radiopharmaceuticals used in nuclear medicine. On a national level, the Dutch medicine authority is the Medicines Evaluation Board (CBG). They are responsible for assessing, monitoring, and promoting the proper use of medications in the Netherlands[60]. The EMA performs a centralised marketing authorisation procedure for most new pharmaceutical products in Europe. If a marketing authorisation is issued by the EMA, the CBG issues the marketing authorisation for the Dutch market.

Where the EMA and CBG focus on safety, quality, and efficacy of medicine, the National Health Care Institute (ZIN) is responsible for assessing and advising on the reimbursement of care within the Netherlands. It evaluates the cost-effectiveness of treatments, medicines, and medical interventions. They provide recommendations to the government regarding what medicine should be reimbursed and under what conditions. These recommendations are based on studies and evidence submitted by the manufacturer in line with Health Technology Assessment (HTA) requirements.

57 Nederlandse Arbeidsinspectie (n.d.). Ioniserende straling.
Source: https://www.nlarbeidsinspectie.nl/onderwerpen/ioniserendestraling
58 RIVM (n.d.). Medische radionucliden.
Source: https://www.rivm.nl/straling-en-radioactiviteit/straling-in-de-gezondheidszorg/medische-radionucliden
59 PALLAS Reactor (2023). Financiering rond bouw PALLAS-reactor.
Source: https://www.pallasreactor.com/nieuws/financiering-rond-bouw-pallas-reactor
60 CBG (n.d.). Source: https://www.cbg-meb.nl/onderwerpen/themas/over-ons-de-organisatie

Once the nuclear medicine is approved, the ministry of Health, Welfare and Sport (VWS) determines the maximum price[61]. The Ministry of VWS guards the efficacy, quality, and risks of medicines, and makes agreements to keep (nuclear) medicines affordable. Once the medicine is in use, the Dutch Medicines Act (GnW) ensures safe medicine use by reporting side effects, creating online prescription rules, and potentially give fines for violation of safety practices in the production, storage, transport of medicinal products. This is monitored by the Health and Youth Care Inspectorate (IGJ).

3.1.3 Industry: development and production

It is rare for a country to have the whole supply chain for nuclear medicine encompassing enrichment, production, processing, and waste processing of nuclear medicine, like the Netherlands does. This is a great strength of the Dutch ecosystem. A vulnerability lies in the concentration of one or a limited number of companies operating in the different links in the value chain[62]. If one of those companies ceases operation, it would pose challenges in finding suitable alternatives to fill this gap. Nevertheless, there is currently no indication that such a scenario is likely to unfold soon. For each link, the type of actor and their role in the supply chain is discussed below.

3.1.3.1 Enrichment and target fabrication

Urenco is involved in the enrichment of stable isotopes that are used to produce medical radioisotopes, and that are also used for developmental and research purposes. It is one of only two companies within Europe that are active in this field and is therefore an asset for the country.

3.1.3.2 Medical radioisotope production and processing

Medical isotopes are mainly produced in nuclear research reactors and cyclotrons, or in some novel accelerator-based neutron sources (e.g. SHINE). In 2022, 16 cyclotrons were operational in the Netherlands[63], often as part of a Dutch hospital and/or university (holding).

There are few industrial actors involved in producing medical radioisotopes in the Netherlands. The main producer of medical radioisotopes in the Netherlands is NRG, which operates the HFR research reactor in Petten. This is one of the largest producers of molybdenum-99 in the world. They produce about 70% of the medical isotopes that are used in European hospitals[64]. Although not currently active yet, SHINE is also going to produce medical radioisotopes in the Nertherlands. Other producers, produce medical radioisotopes with cyclotrons, including GE Healthcare, BV Cyclotron VU and four producers linked to (academic) hospitals. There is also one start-up active in this field, Alfarim, although it is not in operation yet.

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61 Nationale Zorgauthoriteit (n.d.). Hoe worden de tarieven vastgesteld. Source: https://www.nza.nl/documenten/vragen-en-antwoorden/hoe-worden-tarieven-vastgesteld#:~:text=Op%20basis%20van%20de%20Wgp,zijn%20dan%20de%20Wgp%2Dmaximumprijs

62 Tweede Kamer (2022). Achtergrondanalyse ten behoeve van de besluitvorming over de PALLAS-reactor. Source: https://www.tweedekamer.nl/downloads/document?id=2022D36670

63 Technopolis (2022). Productie van medische isotopen met cyclotrons, een vergelijkende studie tussen Denemarken en Nederland. Source: https://www.rijksoverheid.nl/documenten/rapporten/2022/01/31/productie-van-medische-isotopen-met-cyclotrons

64 RTV Noord (2022). Isotopenfabriek Shine in Veendam 'in gevaar' vanwege plannen concurrent Pallas. Source: https://www.rtvnoord.nl/nieuws/923562/isotopenfabriek-shine-in-veendam-in-gevaar-vanwege-plannen-concurrent-pallas

The processing of medical radioisotopes requires a hot lab. This is a facility for working safely with radioactive substances. It is used for instance to couple/label a radioactive substance to a non-radioactive substance[65]. Hot labs are also used to process the medical radioisotopes into a final product, the radiopharmaceutical, and package the product safely. Currently, the number of these hot labs in the Netherlands is limited. Securing access to a hot lab may be an issue for companies (particularly start-ups) that do not have the funds to acquire one. Hot labs are expensive (in the order of millions of euros) and time-consuming (multiple years) to set up. Companies or research institutes may therefore need to look externally for hot lab capacity (for example, within hospitals), but capacity is limited and, as hot labs are often designed to operate for a specific radiopharmaceutical, may not be able to accommodate other products and isotopes. Should the Dutch ecosystem for nuclear medicine grow, then the current hot lab capacity seems not fit to deal with that.

3.1.3.3 Pharmaceutical companies

Pharmaceutical companies are primarily responsible for ensuring the safe production and reliable delivery of medicines. They play a big role in the extensive process of researching and developing new drugs. This is a process characterised by its length, uncertainty, and substantial costs. On average, it takes ten years for a drug to progress from initial discovery to market availability[66]. In the Netherlands, R&D costs for a new medicine are estimated to be 1.13 billion euros[67]. While specific figures for the time and costs associated with radiopharmaceuticals are not available, it is presumed that these are even higher because of stricter (nuclear) regulations, and the need for substantial investments in infrastructure.

In recent years, nuclear medicine in the Netherlands has attracted the attention of large pharmaceutical companies. They operate internationally, often have their headquarters outside the Netherlands, and often entered the Dutch market by acquiring smaller companies that were active in nuclear medicine[68],[69]. Still, there remains a relatively limited number of companies operating in this field within the Netherlands.

3.1.3.4 Equipment suppliers

The Netherlands hosts a notable number of equipment suppliers. We identified 13 of them, acknowledging that this list may not be complete. In contrast to the pharmaceutical companies, these are typically smaller enterprises that specialise in supplying equipment. This often extends beyond nuclear medicine and encompasses a range of medical devices also used for biotechnological research, for example. They supply for measurement, research, and production of radiopharmaceuticals. Additionally, they provide solutions for managing radioactive waste and excretions in the hospitals.

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65 Amsterdam UMC (n.d.). Het Hot lab (Nucleaire Geneeskunde). Source: https://www.amc.nl/web/specialismen/radiologie-en-nucleaire-geneeskunde/radiologie/het-hotlab-nucleaire-geneeskunde.htm

66 Vereniging Innovatieve Geneesmiddelen (n.d.). Geneesmiddelenontwikkeling. Source: https://www.verenigninginnovatievegeneesmiddelen.nl/themas/innovatie/geneesmiddelenontwikkeling

67 Nederlands Tijdschrift voor Geneeskunde (2020). Wat kost onderzoek en ontwikkeling van een medicijn? Source: https://www.ntvg.nl/artikelen/wat-kost-onderzoek-en-ontwikkeling-van-een-medicijn

68 Advanced Accelerator Applications (n.d.). Advanced Accelerator Applications Acquires the IDB Group. Source https://www.adacap.com/advanced-accelerator-applications-acquires-the-idb-group/

69 Terumo Europe (2020). Terumo Acquires Quirem Medical to Enhance its Interventional Oncology Field. Source: https://www.terumo-europe.com/en-emea/news/terumo-acquires-quirem-medical-to-enhance-its-interventional-oncology-field

3.1.3.5 Industry representation

The industry representation can be divided into organisations that represent the pharmaceutical sector (e.g. the VIG) and those that represent the nuclear sector (Nuclear Society). Their role is to represent the pharmaceutical or nuclear industry towards governmental stakeholders and to raise awareness for the issues that companies face in the pharmaceutical and nuclear sectors. In addition, they aim to inform the public and press and contribute to societal debate.

However, when examining the ecosystem of nuclear medicine, the existing industry representations seems to play a limited part. There is no industry representation specifically for the field of nuclear medicine in the Netherlands. This gap may influence the ability to addressing sector-specific issues, and to advocate for the interests of stakeholders in nuclear medicine specifically.

3.1.4 Research organisations

Research in the field of nuclear medicine is conducted throughout the supply chain. It therefore involves various actors: (academic) hospitals, producers, suppliers of equipment, pharmaceutical companies, and research organisations. The nature of research varies depending on the type of actor.

- **Academic hospitals**: academic hospitals predominantly focus on fundamental research and (pre-)clinical studies. The findings of research in academic hospitals can be sold to pharmaceutical companies, who then bring it to market.
- **Hospitals conducting scientific research**: some peripheral hospitals are actively involved in nuclear medicine research, for example the Rijnstate hospital (Arnhem)[70] and St. Antonius hospital (Nieuwegein)[71]. The Antoni van Leeuwenhoek hospital has a separate research institute for cancer research, the Netherlands Cancer Institute, in which also some research in nuclear medicine is conducted.[72].
- **Universities and RTOs**: these conduct more technical research into, for instance, the production of medical isotopes. Both the TU Delft and NRG are active in this type or research.
- **Industrial actors**: entities within the industrial sector conduct research specific to their role in the supply chain. Producers concentrate on developing methods for producing new medical isotopes[73], while pharmaceutical companies explore the creation of new medicines or identify new applications. The top 10 pharmaceutical companies in 2022 spend between 11.5 and 30.9% of their revenue on R&D[74].

70 Rijnstate (2018). Gerenommeerd hoogleraar nucleaire geneeskunde naar Rijnstate. Source: https://www.rijnstate.nl/over-rijnstate/nieuws/2018/gerenommeerd-hoogleraar-nucleaire-geneeskunde-naar-rijnstate/
71 St. Antonius Research & Development (n.d.). Wetenschappelijk onderzoek Nucleaire Geneeskunde. Source: https://www.antoniusziekenhuis.nl/research/onderzoekslijnen/wetenschappelijk-onderzoek-nucleaire-geneeskunde
72 Antoni van Leeuwenhoek (n.d.). Nucleaire Geneeskunde. Source: https://www.avl.nl/voorbereiding-afspraak/afdelingen-en-centra/afdeling-nucleaire-geneeskunde/
73 AlfaRim (n.d.). Actinium-225. Source: https://www.alfarim.com/
74 Statista (2023). R&D spending as revenue share of leading 10 pharmaceutical companies in 2022. Source: https://www.statista.com/statistics/309471/randd-spending-share-of-top-pharmaceutical-companies/

- **Dutch Association for Radiation Protection (NVS)**: NVS aims to promote scientific studies related to the protection of people, animals, plants, and property from radiation. Their activities involve bringing together radiation experts in the Netherlands, to promote the practical application of the knowledge and insights gained about radiation hygiene.
- **Oncode Institute**: this institute is a collaborative initiative of top cancer researchers from various Dutch institutions. Oncode Institute provides a platform for researchers to explore new knowledge freely. Researchers within Oncode Institute have the flexibility to pioneer in their studies. The institute facilitates collaboration among researchers, supports valorisation efforts, and encourages collaboration with the industry. Within Oncode some research in nuclear medicine is conducted, although this is limited to a few projects.

There is thus a diverse research landscape in the Netherlands, with a variety of stakeholders who address diverse issues within the field of nuclear medicine. These research organisations and their activities contribute to the robust academic performance in Dutch nuclear medicine.

3.1.5 Intermediary organisations

When it comes to intermediary organisations, there is a diverse set. Generally, their goal is to facilitate connections between different actors. Who these actors are, differs per intermediary organisations.

The Technology Transfer Offices (TTOs) act as intermediaries between (academic) hospitals or universities and businesses. They are part of the hospitals and are focused on the valorisation of research results. None of these TTOs are specialised in the domain of nuclear medicine, but can provide relevant services for the valorisation of radiopharmaceuticals, either to existing or new businesses. Their services range from handling confidentiality agreements (NDA), assessments of inventions for patenting, management of IP, negotiating collaborative research and licensing contracts with industry, and supporting the creation of start-up companies based on the knowledge of the hospital or university. Several companies have spun out from hospitals and universities through these TTOs, also in nuclear medicine, such as Quirem Medical.

Another type of intermediary organisation that makes the connection between companies and universities or hospitals, are contract research organisations (CRO). CROs focus on supporting (foreign) companies, universities or (academic) hospitals with their applied (bio)medical research, such as clinical trials. CROs are commercial businesses working with businesses and hospitals in clinical trials. In the Netherlands, we identified only two of those companies, Tracer CRO and ICON, with experience or a specialisation in nuclear medicine. Tracer CRO, for example, provides support to foreign pharmaceutical companies in performing their clinical trials in the Netherlands.

The government funded Centre for Future Affordable Sustainable Therapy Development (FAST) focuses on facilitating connections in the whole ecosystem, with a focus on enhancing therapy development. FAST operates as a central hub that brings stakeholders together, links therapy development initiatives, addresses common obstacles in therapy development and prevents fragmentation of R&D activities. Their core activity is to strengthen developments that offer opportunities to improve therapy development.

There are also numerous associations for different healthcare domains which may be relevant for nuclear medicine. These associations bring together professionals engaged in similar work, rather than facilitating connections between different types of actors as the above organisations do. The table below provides an overview of these associations.

Health care domain	Name of professional association	Abbreviation in Dutch
Medical oncology	Netherlands Association for Medical Oncology	NVMO
Radiology	Netherlands Association for Radiology	NVvR
Urology	Netherlands Association for Urology	NVU

Table 2 Identified health care domain associations in the Dutch ecosystem for nuclear medicine

3.1.6 Hospitals and pharmacies

The nuclear medicine departments hospitals are responsible for diagnosis and treatment of patients with nuclear medicine, while the hospital's radiopharmacy prepare nuclear medicine for administration. Hospitals are responsible for maintaining sufficient stock of nuclear medicine and for ensuring the quality of care to the patient[75]. They either buy this medicine from pharmaceutical companies or produce it in-house.

The different professions in hospitals that encounter nuclear medicine in the Netherlands are organised in professional associations. These professional associations have multiple tasks. They advocate the interests and rights of their members, can provide networking opportunities, provide information and resources, or offer training programmes and seminars for the professional development of their members. Some are open to all professions that encounter nuclear medicine, others are specific to one profession but are not only available for nuclear medicine. The following table provides an overview of the professional associations in the Netherlands. This list might not be complete but can be used for illustration.

Profession	Name of professional association	Abbreviation in Dutch
Clinical physicist	Dutch Association for Clinical Physicists	NVKF
Radiochemistry	Netherlands Clinical Radiochemistry Association	NKRV
Pharmacist	Netherlands Association of Hospital Pharmacists	NVZA
Multidisciplinary[76]	Dutch Association for Nuclear Medicine	NVNG
Multidisciplinary	PSMAForum	PSMAForum

Table 3 Identified professional associations in the Dutch nuclear medicine ecosystem

75 Tweede Kamer (2022). Achtergrondanalyse ten behoeve van de besluitvorming over de PALLAS-reactor. Source: https://www.tweedekamer.nl/downloads/document?id=2022D36670

76 According to the website, they are open to nuclear physicians, (nuclear) radiologists, hospital pharmacists, clinical physicists, and clinical radiochemists.

Nuclear medicine is organised differently within various hospitals. Firstly, the integration of nuclear medicine within hospital departments varies. Some hospitals combine nuclear medicine with radiology in a single department, such as Amsterdam UMC and Erasmus MC. Other hospitals embed nuclear medicine within the imaging department, such as Radboudumc. There are also hospitals where nuclear medicine is a standalone department, for example at Ziekenhuisgroep Twente and the Antoni van Leeuwenhoek hospital. Secondly, the role of the nuclear medicine physician in hospitals differs. Patients are admitted under the responsibility of an internist in some hospitals, while other hospitals place patients directly under the care of a nuclear medicine physicians.

3.1.7 Patients

There are multiple and diverse patient organisations in the Netherlands, often aimed at a specific disease. Here only a few are mentioned, namely those organisation of which patients particularly benefit from nuclear medicine.

Within the realm of nuclear medicine, two particularly relevant organisations are the Dutch Federation of Cancer Patients Organisations (NFK) and the Prostate Cancer Foundation. NFK serves as an umbrella organisation for 21 cancer patient organisations. They represent the overarching interests for all their patients and aim for a better quality of life, healthcare, and better access to healthcare for (ex) cancer patients and their loved ones. They also offer contact with peers. As part of this, they for example include the voice of the patient in scientific research and guidelines. The Prostate Cancer Foundation has a similar aim, although meant to support patients with prostate cancer specifically.

Patients themselves are becoming increasingly aware of new methods that might work for their condition via the internet[77]. According to the interviews, they inquire more often whether certain methods, possibly nuclear medicine, would work for them. Oncology patients often experience a lot of side effects from their treatment. If a method using radiopharmaceuticals causes less side effects, patient organisations can support the introduction of that method into treatment guidelines.

3.2 Key characteristics of the innovation ecosystem

In this paragraph we describe key characteristics of the innovation ecosystem. These are based on both interviews and desk study. Where possible, characteristics will be further described using quantitative data, both from third party reports and the conducted mini survey.

3.2.1 Diagnoses and treatments in the Netherlands

Radiopharmaceuticals are used to diagnose and treat 10 million patients per year in the EU, of which 65% are in the oncology area[78]. A total of over 338.000 nuclear medicine

77 Radboudumc (2014). Patiënt blijkt beter geïnformeerd met sociale media. Source: https://www.radboudumc.nl/nieuws/2014/patient-blijkt-beter-geinformeerd-met-sociale-media

78 EMA (2021). Report of EMA-Nuclear Medicine Europe bilateral meeting, 23 September 2021. Source: https://www.ema.europa.eu/en/documents/report/report-european-medicines-agency-nuclear-medicines-europe-meeting_en.pdf

examinations were performed in Dutch hospitals in 2020. This is a 3% decrease compared to 2019. The figure below shows trends in nuclear medicine examinations[79].

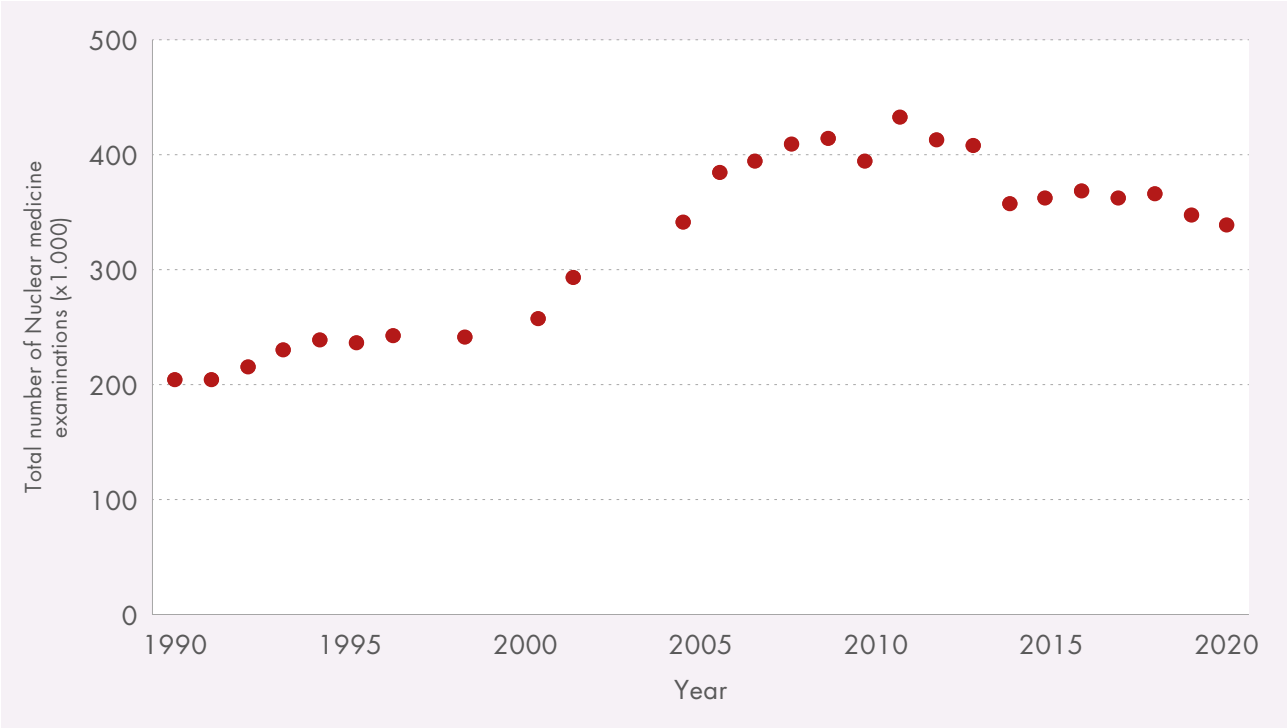

Figure 4 **Nuclear medicine examinations per year**
Source: RIVM (2023), see footnote 79. Edited by Technopolis Group.

The ANVS reports[80] that on a yearly basis, around 4.800 treatments with radioactive substances are performed in Dutch hospitals.

3.2.2 Facilities and infrastructure

3.2.2.1 Medical radioisotope production

In terms of medical radioisotope production facilities, the Netherlands has a strong position and is realising new facilities., The HFR reactor in Petten, operated by NRG, is a large supplier of medical radioisotopes in the Netherlands and the EU. This reactor will be replaced by the new PALLAS reactor in the future. SHINE is currently developing a radioisotope production site in Veendam. In addition, there are currently several cyclotrons producing radioisotopes for medical application.

79 RIVM (2023). Trend in the number of nuclear medicine examinations. The break in trend from 2014 onwards is caused by the exclusion of bone densitometric examinations, which are included in the statistics before 2014. Source: https://www.rivm.nl/medische-stralingstoepassingen/trends-en-stand-van-zaken/diagnostiek/nucleaire-geneeskunde/trend-in-aantal-nucleair-geneeskundige-onderzoeken#:~:text=Het%20aantal%20nucleair%20geneeskundige%20onderzoeken%20voor%20de%20jaren%201991%20tot,uitgevoerd%20in%20de%20Nederlandse%20ziekenhuizen

80 ANVS (2023). Annual Report 2022.
Source: https://www.autoriteitnvs.nl/documenten/jaarverslag/2023/03/15/jaarverslag-anvs-2022

Medical cyclotrons in the Netherlands mainly supply 18F products. Radboud Translational Medicine (Nijmegen), Cyclotron Noordwest (Alkmaar) and BV Cyclotron VU (Amsterdam) have a larger portfolio of products: ^{13}N is produced in Nijmegen and Alkmaar, ^{11}C is produced in Nijmegen, and ^{89}Zr and $^{81}Rb/^{81m}Kr$ generators are produced in Amsterdam. UMCG in Groningen produces mainly products for internal use and for clinical studies. Almost all products produced/supplied are used for PET tracers, all known products from these cyclotrons are used in diagnostics. Cyclotrons are distributed across the country with most cyclotrons in the Randstad.

Regarding medical radioisotope production, security of supply issues have been mentioned, although these should be addressed by PALLAS and SHINE in the future.[81] Production of small/research quantities for novel medical radioisotopes may however be limited and expensive.

3.2.2.2 R&D and hot labs

R&D is conducted by several actors and is considered one of the major strengths in the Netherlands' ecosystem.

Academic researchers are currently the main driver in R&D in the Netherlands, developing radiopharmaceuticals and applications. Clusters of researchers (and in a growing degree commercial spin offs) are situated around cyclotrons and focus on R&D in medical radioisotopes, radiopharmaceuticals, and the use thereof. NRG-PALLAS is a main player in the R&D of medical radioisotope production. Its FIELD-LAB facilities aim to collaboratively organise research with several academic centres.

While the R&D landscape is one of the major strengths of the Dutch ecosystem, interviewees stress the importance of further collaboration and integration of R&D activities, both within stages of the process for nuclear medicine development (i.e. collaboration between academic researchers) as well as across stages in this process (linking and integrating isotope production, academic research, and market access by commercial parties). Collaboration and interlinking of stages will be discussed in 3.2.4.

Several of the interviewed university representatives mention there is a high demand for (hot) labs that can process nuclear material. These are in demand by companies that need the facilities to test new therapies and applications, but do not have (and cannot afford) these expensive facilities themselves.

One of the particular strengths of the ecosystem – as mentioned by interviewees – is the amount of new pharmaceutical businesses, startups and spinoffs arising around the different cyclotrons and academic R&D facilities. While it is hard to fully quantify the amount of actual companies that come forth out of these sites (as they sometimes are not even registered yet as companies at the chamber of commerce), interviewees claim more companies will establish themselves given the possibilities around new therapies using medical radioisotopes. A successful example of a pharmaceutical company that originally spun out from Utrecht UMC is Quirem Medical.

81 NucAdvisor (2021). Co-ordinated Approach to the Development and Supply of Radionuclides in the EU. Brussel: European Commission.

3.2.2.3 *Medical facilities*

Patient treatment centres for nuclear medicine need to have specific infrastructure, as patients are loaded with nuclear materials for treatment. Sufficient safety and procedural standards and infrastructure to accommodate these treatments are needed, to protect medical personnel, for transportation of nuclear materials and for nuclear waste or material disposal.

While there are several treatment centres for nuclear medicine in the Netherlands, the total capacity of treatment centres in considered to be not fully future proof. An increase in nuclear medicine treatment is expected (both for medicine testing and for approved therapies)[82],[83]. Demand for such treatment centres provides possibilities for the future – it is suggested by several interviewees to invest in a centralised medical treatment centre, to accommodate nuclear medicine testing and patient treatments. Centralising medical treatment is considered efficient as well as contributing to improved collaboration between hospitals and researchers.

3.2.3 Funding and investments

Lack of funding is considered to be a major bottleneck in the development of the sector. While the Dutch government has invested majorly in the PALLAS reactor (cumulatively over €1.5 billion in the last years) and supports the construction of the SHINE production facility for medical isotopes in Groningen (investing around €10 million through several programmes), the general consensus among interviewees is that funding possibilities are too limited for both academia and business to create an accelerated growth path of the sector in a broad and sustainable sense. Participants in the mini-survey regard access to funding one of the parts of the Dutch ecosystem that can be improved the most.

Almost three quarters of the respondents of the mini survey do not rate the funding and investment climate higher than 'neutral'.

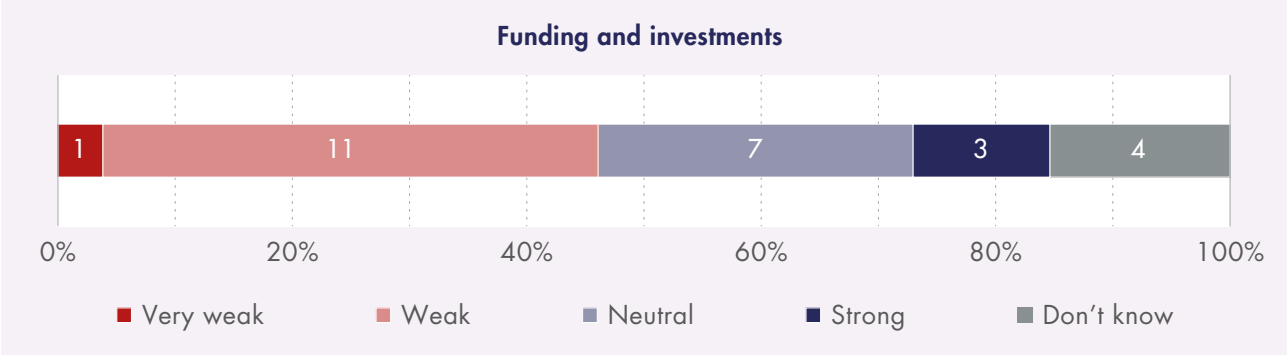

Figure 5 Rating of the funding and investments in Nuclear Medicine in NL

Source: Survey among NL Stakeholders in Nuclear Medicine by Technopolis. Numbers represent amount of respondents that selected the answer category.

82 Technopolis Group (2021) - Study on sustainable and resilient supply of medical radioisotopes in the EU - Therapeutic Radionuclides

83 This has been consistently voiced by interviewees, also from abroad.

Interviewees point out that access to funding in several other countries (such as Belgium, US, and Canada) is generally better. Currently, combinations of public/private co-financing in infrastructure in the Netherlands is most common. Cyclotrons currently installed in the Netherlands have received limited direct public funding. Most are commercially funded and/or are funded by universities or hospitals, supported by small tickets of direct public funding. BV Cyclotron VU, AccTec BV (GE Healthcare) and Curium are fully commercial suppliers of diagnostic radiopharmaceuticals, most of the other suppliers are part of a hospital and produce primarily for in-hospital or regional use.

While academia receives support through national and international programmes (provided by ZonMW, NWO and EU programmes), interviewees describe the funding as too small, fragmented (funding researchers who develop their own methods and treatments separately, creating 'detached' and competing entities) and too short term oriented. Looking at the value chain, academic funding is primarily aimed at stage 1.1 (fundamental or basic research) and 1.2. preclinical research. Large scale funding needed for stages 1.3 Translational research and 1.4 Clinical Research is considered to be lacking.

For businesses, the Dutch government has several programmes and policy instruments. Examples are Regional Development Funds (ROMs, which are government funds under the oversight of Provinces) and several startup subsidies, tax deductions, grant schemes and loans such as Early-Stage Financing[84] (VFF), WBSO[85] and MIT[86]. In general, the ticket sizes of these programmes are considered to be too small for the large and capital-intensive investments needed in the pharmaceutical sector. Schemes by the ROMs are of greatest interest, since ticket sizes are larger than most national grants and schemes.

Currently, the national Growth Fund (Groeifonds) programme provides possibilities for a large capital injection in the sector. However, this program is likely to run for four years, after which the opportunities for investments of such magnitude might decrease again.

Both academia and business show a demand for a more large-scale funding of the sector. Sufficient long term government funding is highly important for the sector, as private funding can be cautious or hesitant due to the long investment horizon (it can take decades for investments to show returns) and high risks in the sector.

3.2.4 Innovation culture: risks, openness, and collaboration

There are several cultural factors that have a positive effect on innovation, openness, and collaboration, but also several that have a stifling effect.

3.2.4.1 Innovation culture in general

First, the innovation culture in the Netherlands is regarded very forward thinking and state of the art. Academic research produces many different possible applications for nuclear medicine – which is attributed to the strong culture and history the Netherlands has in this

84 See: https://www.rvo.nl/subsidies-financiering/vff
85 See: https://www.rvo.nl/subsidies-financiering/wbso
86 See: https://www.rvo.nl/onderwerpen/mit

field. The presence of a lot of infrastructure (such as the Petten reactor, cyclotrons, active research departments et cetera) clusters knowledge and talent in the Netherlands.

3.2.4.2 *Collaboration, openness, and information sharing*

Collaboration is a peculiar subject in the innovation culture. On one hand, actors in the ecosystem stress the fact that collaboration in general is seen as strong – many actors know each other, and it is not uncommon to approach others for collaboration (both in academia and between academia-businesses). At the same time, collaboration is considered one of the factors that can be improved greatly.

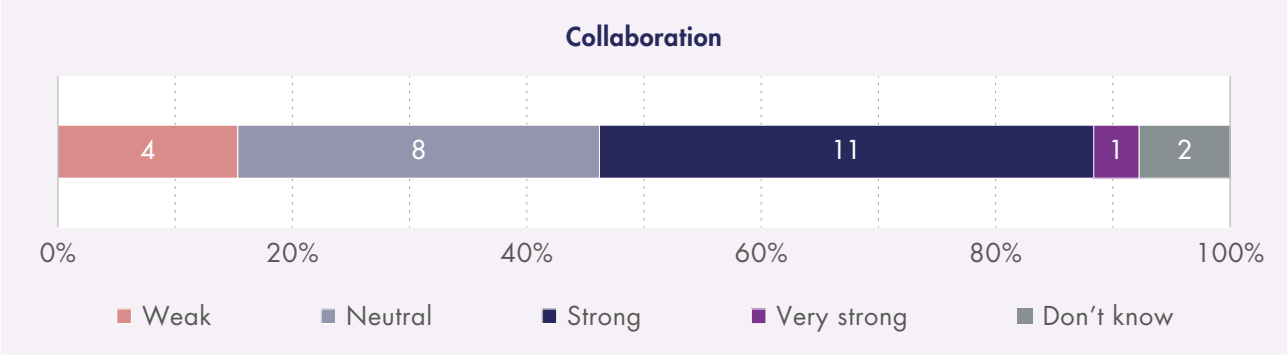

Figure 6 **Rating of the collaboration in Nuclear Medicine in NL**

Source: Survey among NL Stakeholders in Nuclear Medicine by Technopolis. Numbers represent amount of respondents that selected the answer category.

Within academia, there is a sense that different researchers have their own priorities, subjects and programmes and that output of academia can be improved by fostering collaboration. Currently, academia is somewhat fragmented. Academic researchers compete for grants which – combined with the pressure to produce academic papers in highly regarded scientific journals – is a disincentive for collaboration.

Collaboration between links in the value chain (consisting of producers of isotopes, academia, and businesses) can be greatly improved as well. To illustrate: academics indicate that the supply of isotopes needs to be consistent and continuous. Producers however can provide this steady supply in the situation where they have a guarantee that the isotopes are continuously used by academic researchers. However, due to the fragmented nature of academia, this is not always the case. Looking at the relation between academia and business, we see similar examples. Businesses that want to bring therapies to the market need these therapies checked by several regulatory requirements. This means that businesses need to inform researchers of or TTOs need to train researchers in these requirements, so that researchers can set up their research in such a way that these therapies are compliant with regulations. Many interviewees indicate that such forms of collaboration need to be further invested in to create a more streamlined value chain.

Collaboration between nuclear medicine and other medical disciplines (within hospitals) can also be improved, especially the collaboration between nuclear medicine specialists and oncologists, urologists, cardiologists, and neurologists. Improving understanding of each

other's worlds, practices and possibilities can be beneficial in furthering patient care and treatments.

While some aspects of collaboration are rated highly, there are (at the same time) risks. Competition and access to funding and investment are main issues in different parts of the value chain. Academics are competing for grants, isotope producers are competing for government investments and researchers and companies developing new therapies are competing for market access. Several interviewees mention that a coherent long-term vision and platform for stakeholders to collectively coordinate and align efforts to strive for common goals to further strengthen the sector should be developed.

The figure below shows the rating of openness & information sharing in the field in the Netherlands.

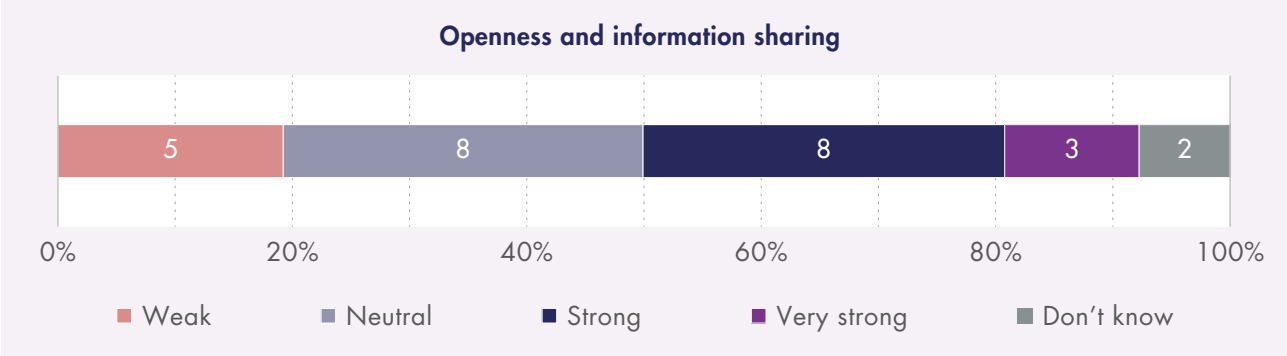

Figure 7 **Rating of the openness and information sharing in Nuclear Medicine in NL**

Source: Survey among NL Stakeholders in Nuclear Medicine by Technopolis. Numbers represent amount of respondents that selected the answer category.

3.2.4.3 Risk taking

Risk taking is considered to be poor in the Netherlands. Both the results of the mini survey and the interviews show similar results.

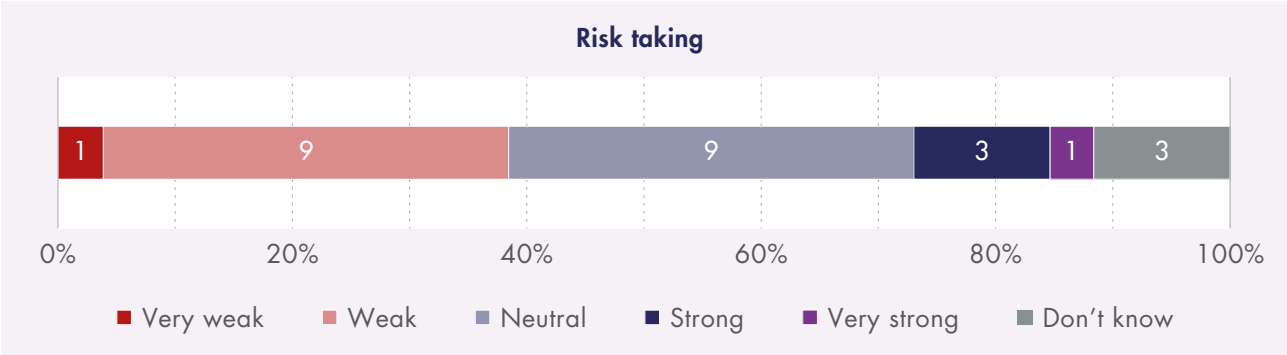

Figure 8 **Rating of risk taking in Nuclear Medicine in NL**

Source: Survey among NL Stakeholders in Nuclear Medicine by Technopolis. Numbers represent amount of respondents that selected the answer category.

3.2.5 International connections

The Dutch ecosystem is characterised as highly connected on the international level. This applies to both the innovativeness as earning capacity stages in the value chain.

The position of Dutch academia in the international science field is regarded as strong by interviewees. Analysis of international collaboration in nuclear science and technology in 2006-2015 shows that the Netherlands (together with Belgium and Switzerland) holds the highest international collaboration rates of around 70%[87]. Germany, USA, and France were the centres of the collaboration network. The Netherlands is reported as 9th in the world when looking at the number of publications (i.e. scientific output) in the field of "Radiology, Nuclear medicine and Medical Imaging" over the period of 1986-2010[88]. In general, the Netherlands is regarded as well represented in international conferences and publications and has an image of being highly innovative and forward thinking in the field.

Results of the mini survey also show the strong perceived international connectedness.

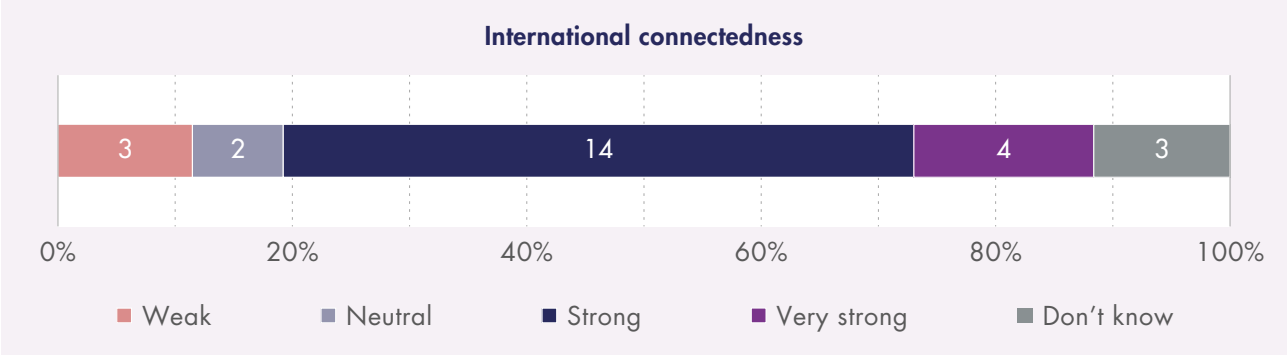

Figure 9 **Rating of the of the international connectedness of NL Nuclear Medicine ecosystem**

Source: Survey among NL Stakeholders in Nuclear Medicine by Technopolis. Numbers represent amount of respondents that selected the answer category.

The international connectedness in the earning capacity stages (stages 3 and 4 in Figure 2) is strong as well. Recent investments in PALLAS and the establishment of SHINE have put the Netherlands further on the map for other businesses. Also, the presence of several international governing bodies (such as the EMA in Amsterdam) is considered to be an asset in the sector.

3.2.6 Personnel, employees, and talent

The quality of personnel in the field of nuclear medicine in the Netherlands is considered among the best in the world. This applies to all the different steps in the production chain. The high quality of personnel is one of the main reasons for foreign companies to establish branches in the Netherlands.

87 Fu, H. Z., Chu, J., & Zhang, M. (2018). In-depth analysis of international collaboration and inter-institutional collaboration in nuclear science and technology during 2006–2015. Journal of Nuclear Science and Technology, 55(1), 29-40.

88 Y.J. Ku et al. (2012). Korea's Contribution to Radiological Research Included in Science Citation Index Expanded, 1986-2010. Korean J. Radiol. 2012, 13(5), 523-529.

There are several education programmes in the field of nuclear medicine. Physicians in training ("artsen in opleiding tot specialist, or AIOS") can be trained as nuclear medicine experts[89] when specialising. There are also education programs for medical nuclear workers at training programs "medical imaging and radiotherapy techniques (MBRT)". In the Netherlands, the eight academic hospitals and four more peripheral hospitals offer nuclear medicine training. Next to these specific trainings, aimed at nuclear medicine and nuclear applications in medicine, there is a plethora of education programmes related to nuclear technology, engineering, and physics.

At the same time there are challenges regarding personnel, employees, and talent. Shortages of qualified personnel is regarded by many as a major threat. To further accommodate the foreseen growth of the sector, steps need to be taken to improve influx of new personnel.

The results of the mini-survey show the mixed rating of the labour market – 60% of the respondents rate 'labour market & personnel' as neutral or lower.

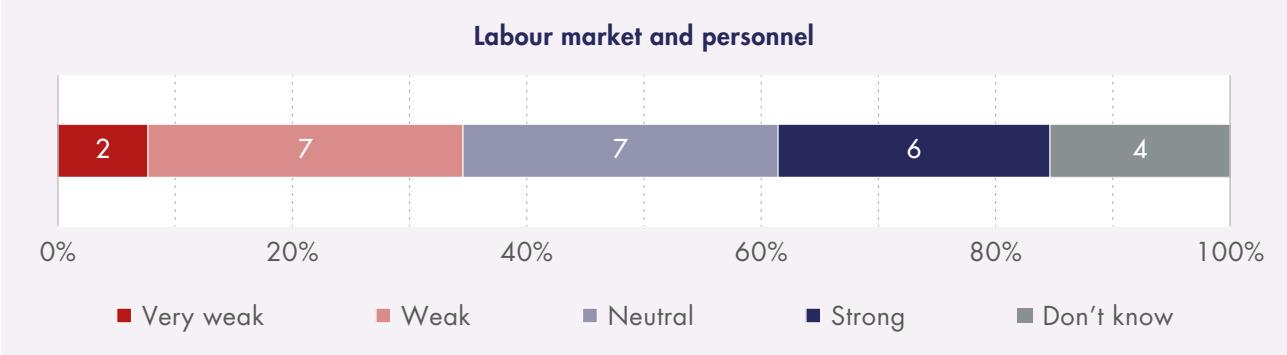

Figure 10 Rating of the labour market and personel in NL

Source: Survey among NL Stakeholders in Nuclear Medicine by Technopolis. Numbers represent amount of respondents that selected the answer category.

The sector – especially regarding fundamental research – is seen as rapidly ageing. Many researchers – while still very productive – are at the end of their professional careers. In our research, a picture emerges in which the influx of new researchers is relatively modest compared to other medical fields.

This relatively modest influx has several causes. Nuclear medicine is still regarded as a relatively 'niche' medical subject. Furthermore, nuclear medicine has physical, (bio)chemical as well as medical aspects. This means new researchers and practitioners can come from different backgrounds and need a combination of interests and skills to advance in the field. Lastly, the position of the nuclear medicine physician in the hospital is not as strong as more classical or traditional positions such as heart surgeon. Because of the specialised environment (which often physically locates nuclear medicine practitioners 'away' from more

89 In the Netherlands they will become nuclear radiologists instead of nuclear medicine physicians.

traditional medicine, due to regulations regarding the nuclear materials), several researchers and practitioners have indicated the field is somewhat overlooked by others. Combined, these factors indicate the image of the field is not as strong as it can potentially be for new students.

Results of the mini survey also show the relatively poor perceived image of the nuclear sector in the Netherlands.

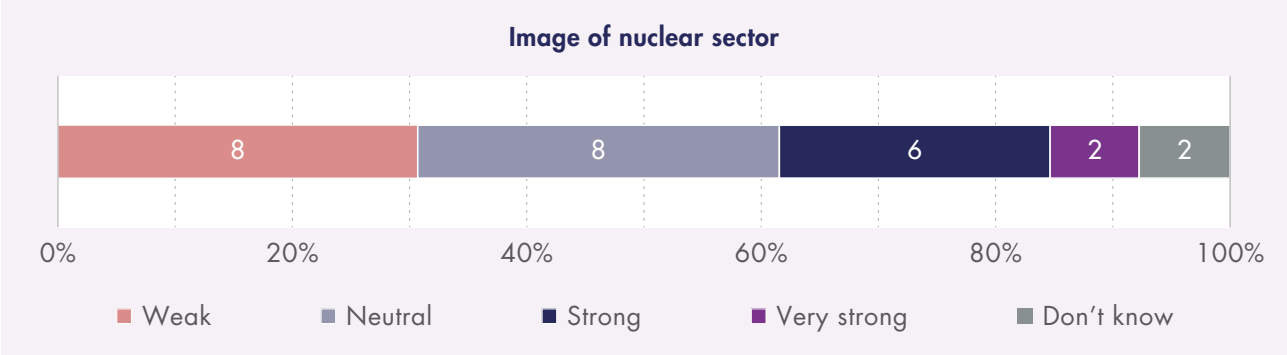

Figure 11 Rating of the image of the nuclear sector in NL

Source: Survey among NL Stakeholders in Nuclear Medicine by Technopolis. Numbers represent amount of respondents that selected the answer category.

Overall, stakeholders (from academia, pharma companies, government, and other perspectives) agree and highly recommend to further advance and improve the image of nuclear medicine to generate a higher influx of new researchers and practitioners in nuclear medicine.

Lastly, several interviewees are critical of integrating education programmes for nuclear medicine and radiology in the Netherlands. The expected increase in nuclear medicine therapies creates a demand for specialists with a combination of therapeutic and nuclear medicine background. With a - current - strong emphasis on diagnostics in training, there is a risk of a shortage of personnel with therapeutic background.

3.2.7 Regulatory frameworks

Regulations and regulatory culture in the Netherlands are by many interviewees regarded as stifling. Interviewees point out that other countries (such as the US) have considerably shorter permit and licencing processes. This is experienced by producers of isotopes, academia (whose nuclear facilities and labs are subject to complex regulations) and businesses alike. In addition, EU directives relevant to the development of nuclear medicine are said to be implemented more stringent in the Netherlands than in other EU countries. Also, the Dutch procedure with medical-ethical committees for early phase clinical research is mentioned to be more restrictive and slower than on some other EU countries.

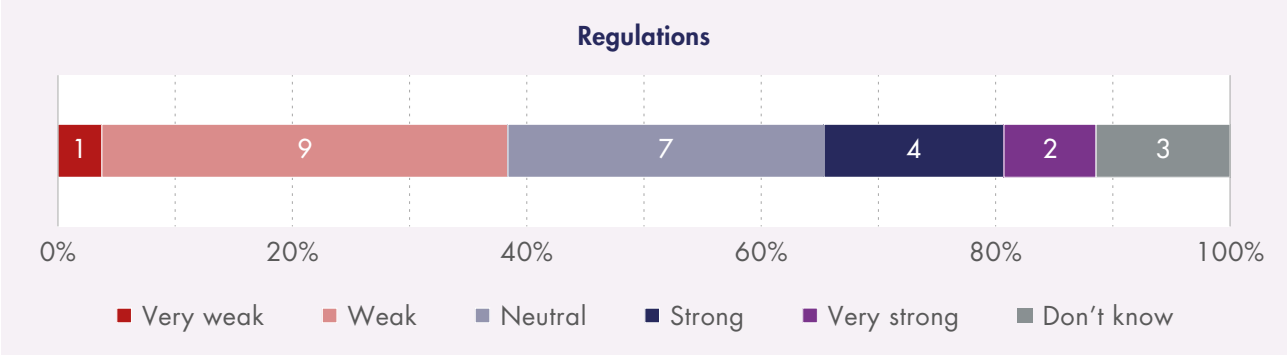

Figure 12 **Rating of regulations in NL**

Source: Survey among NL Stakeholders in Nuclear Medicine by Technopolis. Numbers represent amount of respondents that selected the answer category.

3.3 Strengths and weaknesses

3.3.1 Strengths

The nuclear medicine ecosystem in the Netherlands has three main strengths.

Firstly, the Netherlands boasts a **high standard of academic research in nuclear medicine**. Numerous publications on fundamental research in this field emanate from Dutch researchers. There are enthusiastic and proud researchers involved in this field that can attract more people to nuclear medicine. Additionally, an emerging trend noted by some interviewees is an increased emphasis on collaboration in recent years. This collaborative spirit seems more ingrained in the academic culture of the Netherlands compared to, for instance, the United States.

This, coupled with the presence of a highly educated population, serves to build a robust international reputation. A positive standing on the global stage, in turn, can act as a magnet for international students and professionals seeking to engage in nuclear medicine research. The Netherlands was ranked 9th globally in terms of publications within the radiology, nuclear medicine, and medical imaging domain from 1986 to 2010[90]. Dutch researchers are also often present at international conferences. This way, the Netherlands sustains its position as **international frontrunner**.

Thirdly, the Netherlands benefits from the **availability of (rare) facilities**. Rarely found elsewhere, the presence of facilities such as Urenco's enrichment facility and PALLAS, one of the world's largest producers of medical isotopes, positions the country at the forefront of nuclear medicine research and production. Additionally, the widespread availability of cyclotrons for research and production purposes is a noteworthy asset. The compact size of the Netherlands is an additional advantage in this context[91]. The shorter distances between these facilities play a pivotal role when dealing with radiopharmaceuticals characterised by a limited shelf life. This contrasts with the expansive geography of for example the United States.

90 Y.J. Ku et al. (2012). Korea's Contribution to Radiological Research Included in Science Citation Index Expanded, 1986-2010. Korean J. Radiol. 2012, 13(5), 523-529.

91 According to interviews

This geographical proximity facilitates more efficient collaboration within the nuclear medicine community in the Netherlands.

3.3.2 Weaknesses

Within the Dutch ecosystem for nuclear medicine, there are notable weaknesses that warrant attention as well.

Firstly, a vulnerability lies in the **valorisation of nuclear medicine** in the Netherlands. Despite promising discoveries in academic research, there is often a disconnect in translating these findings into market entries. This is a complex issue. Since researchers are not primarily focused on commercialisation, bringing their discoveries to market is often an afterthought[92]. Consequently, there is often no application for intellectual property (IP) protection, or it occurs too late. This allows academic discoveries made in the Netherlands to be commercialised elsewhere. The lack of emphasis on commercialisation during research further results in limited information sharing between academia and industry. This can lead to a misalignment between research focus and market demand. It can also slow down the process of market entry, as shown by instances mentioned in the focus group where companies inheriting research from academia had to repeat studies due to a lack of clarity on the necessary steps to bring a medicine to market.

A key issue is the **lack of collaboration and joint action** in the field. This occurs on various levels. As mentioned earlier, fostering more collaboration between academics and industry could speed up the process of bringing innovations to the market. This need for collaboration is also evident within hospitals. Different departments that are involved in patient care, such as internists, oncologists, and nuclear medicine specialists, often operate independently when it comes to nuclear medicine. Encouraging these professions to work together on new applications and medications, could result in a more widespread appreciation and usage for that medicine. It is crucial for the patient to be included in this collaborative effort, possibly represented by patient organisations that advocate for their interests. This way, nuclear medicine becomes more tailored to their needs. Informed patients are possibly also more likely to request specific medicines from their doctors when they are aware of the potential benefits and value of such medicine. This approach, already common in oncology, involves patients early in the process of developing and testing medicine.

An important aspect to keep in mind is the **limited capacity of hospital infrastructure**. For the nuclear medicine market to grow, there must be enough facilities equipped to administer the treatments. However, implementing such treatments necessitates dedicated hospital rooms with lead lining, facilities for radioactive waste, wastewater tanks, separate toilets, and laboratories for medicine preparation. This would require investments from hospitals, but the uncertainty surrounding future demand for radiopharmaceuticals makes it challenging to persuade hospital board to commit to these expenditures.

92 According to interviews

In addition, we noticed that **patient organisations are not well organised in relation to nuclear medicine**. Most patient organisations are organised around a specific disease. Nuclear medicine is most relevant to cancer patient organisations. However, most of these organisations have limited knowledge of the field of nuclear medicine, although during this study they have indicated interest in the therapeutic developments in nuclear medicine. In the Netherlands, the Prostate Cancer Foundation (Prostaatkankerstichting) seems to be most knowledgeable about nuclear medicine, following closely the developments related to PSMA labelled radiopharmaceuticals. For the development of radiopharmaceuticals it is important to involve patients and patient organisations timely. That requires to build stronger relations between nuclear medicine and patient organisations.

Lastly, the **regulatory system** in the Netherlands is considered by consulted ecosystem actors a hurdle to the development and market access of radiopharmaceuticals. Permit processing times are notably lengthy, particularly when compared to the more expeditious procedures in the United States. A potential factor that contributed to these delays were capacity issues within regulatory bodies. The need for more dialogue between regulators and those who require permits was emphasised during focus group discussions. Such dialogues could facilitate a mutual understanding of needs and potentially streamline the process for more efficient development and marketing. The duration that IP is valid and maintained is also a factor that hinders the development and marketing processes. IP rights need to be valid and maintained (in multiple countries) before the completion of the development phase, at least until phase I clinical studies. Applying for patents in multiple countries and maintaining these patents can be costly, but important for investors and for improving earning capacity. Extending this to phase II could increase the value of the developed product, which makes it more appealing and easier for industry to adopt.

3.4 Opportunities and threats

3.4.1 Opportunities

An opportunity arises from the **anticipated advancements in nuclear medicine research**. Nuclear medicine is a rapidly evolving field. While radionuclides for diagnostic purposes have been in use for a longer period, recent developments indicate a shifting focus towards therapeutic applications. Depending on the outcomes of these advancements, it holds the potential to establish a new standard in cancer treatments. This shift could lead to a reduction in side effects for patients undergoing treatment compared to current common methods. Although it is now mainly in use in prostate cancer treatments, there is optimism that this therapeutic approach may extend to other types of cancer as well[93].

93 As mentioned in interviews.

Another substantial opportunity stems from the **strategic aspiration to achieve EU independence in terms of radioisotope supply**. This objective is outlined in the Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) by the European Commission in 202[94]. The primary aims include to secure the supply of medical radioisotopes by reducing EU's dependence on foreign suppliers and by accelerating the development of new radioisotope production methods. According to the Euratom Supply Agency (ESA), the EU is still large dependent on enriched isotopes from Russia[95]. ESA underscores that the European capacity for enrichment of source materials and stable isotopes needs strengthening. There is an opportunity for the Netherlands to play a pivotal role in filling this gap.

Lastly, a big opportunity for the ecosystem arises from the current momentum driving further action. There is increasing attention towards nuclear medicine. The Ministry of VWS has earmarked €320 million for investment in PALLAS[96], pending approval from the European Commission with regards to state interference. Simultaneously, strategic plans are underway to submit a National Growth Fund request for DECISIVE (Dutch Medical Isotopes Save Lives). The aim of this initiative is to improve and expedite the development of innovation and business activities in Dutch nuclear medicine. Currently, preparation for the application is in progress. Furthermore, Professor Wim Oyen assumed the role of quartermaster for medical isotopes in September 2023. He is commissioned by the Ministry of VWS to facilitate the academic development of radiopharmaceuticals in the Netherlands. To achieve this, he will develop a roadmap to establish a strategic, long-term vision that is supported by stakeholders within the system. Hence, the Dutch nuclear medicine sector is progressing, and can propel this forward momentum.

3.4.2 Threats

One of the biggest threats to the Dutch ecosystem is the **uncertainty in the supply chain**. This is related to the opportunity that was mentioned above of EU's aspiration to become independent in terms of radioisotope supply. The EU is still very dependent on especially the following countries[97]:

- China as the largest supplier of raw materials, for the extraction and processing of raw materials (especially rare earth elements) to produce various medical radioisotopes.
- South Africa to produce the very rare Iridium.
- Russia for cyclotron enrichment of various target materials (notably lanthanides).
- The United States for the supply of low-enriched uranium, which is necessary for the fuel and targets of the research reactors such as PALLAS.

94 European Commission (2021). SAMIRA Action Plan. Source: https://energy.ec.europa.eu/topics/nuclear-energy/radiological-and-nuclear-technology-health/samira-action-plan_en
95 NUCNET (2023). EU's Strong Position Under Threat From 'Foreign Dependencies'. Source: https://www.nucnet.org/news/eu-s-strong-position-under-threat-from-foreign-dependencies-10-2-2023
96 Rijksoverheid (2024). Plan kabinet: nieuwe kernreactor voor medische isotopen. Source: https://www.rijksoverheid.nl/onderwerpen/straling/plan-kabinet-nieuwe-kernreactor-voor-medische-isotopen
97 Technopolis (2023). Analyse waardeketens en grondstoffen voor medische isotopen, in opdracht van EZK.

Russia's invasion of Ukraine has drawn fresh attention to the fragility of the supply chains for isotopes. At moments of shortages, there is the risk that these countries might export less of these raw materials or for a much higher price. The patients that are depending on their medication might then not have access to them anymore. This is a significant threat.

Another threat that was very frequently mentioned, is the **growing shortage of qualified staff**. Employees in the Netherlands are very knowledgeable, but staff shortage is a growing problem in healthcare. Meanwhile, the demand for care is increasing and this will most likely not change in the coming years[98]. As a result, the quality and accessibility of care in the Netherlands are under increasing pressure. Working in nuclear medicine requires a multidisciplinary approach. Even if there is an expert in the field, it might take a few years to fully get them up to speed on the specifics of one medical isotope. This is also related to the issue of visibility. Nuclear medicine is not a well-known possibility for potential employees or medicine students. Since 2015, nuclear medicine training has been integrated into the radiology study programme in the Netherlands[99]. This integration means essentially that students are predominantly trained as radiologists, with an emphasis on diagnostics. However, the field on nuclear medicine holds significant promise in therapeutics. The existing education does therefore not align with the (future) needs of the field.

Overall, the innovation ecosystem in the Netherlands demonstrates considerable strength. However, the earning capacity has not yet reached that same level. The table on the next page provides a concise summary of the aforementioned information.

98 IGJ (2022). Personeelstekorten in de zorg. Source: https://www.igj.nl/onderwerpen/personeelstekort
99 KNMG (2021). Nucleaire geneeskunde.
Source: https://www.knmg.nl/ik-ben-geneeskundestudent-1/beroepskeuze-vervolgopleiding/nucleaire-geneeskunde-1

SWOT	
Strengths	**Weaknesses**
• **High standard of academic research in nuclear medicine** [innovativeness] – Strong international reputation – Highly educated population • **International frontrunner** [innovativeness] – Strong reputation abroad • **Availability of (rare) facilities** [innovativeness/ earning capacity] – Enrichment facility and one of the world's largest producers of medical isotopes – Geographical proximity between the facilities	• **Commercialisation of nuclear medicine** [earning capacity] – Commercialisation is an afterthought for researchers – Requesting IP is done too late or not at all – Lack of alignment between research focus and market demand • **Regulatory system** [innovativeness/earning capacity] – Regulatory delays (permits take long) – Strict regulation and lengthy procedures • **Limited capacity of hospital infrastructure** [innovativeness] – More capacity requires in investments expensive infrastructure – Difficult to convince hospital board to make that investment when future demand is uncertain • **Patient organisations are not well organised in relation to nuclear medicine** [innovativeness] – A stronger and timely involvement of patient organisations is beneficial for radiopharmaceutical development
Opportunities	**Threats**
• **Anticipated advancements in nuclear medicine research** [innovativeness/earning capacity] – New therapeutic applications – Fewer side effects for the patients • **Strategic aspiration to achieve EU independence in terms of radioisotope supply** [earning capacity] – SAMIRA action plan – Strengthen the European capacity for enrichment of source materials and stable isotopes	• **Uncertainty in the supply chain** [earning capacity] – Dependence on China, South Africa, Russia and the United States for raw materials and enrichment – As showcased by Russia's invasion of Ukraine • **Growing shortage of qualified staff** [earning capacity/innovativeness] – Coupled with increasing demand for care – Requires a multidisciplinary approach – Not a well-known field for potential employees

Table 4 **Summary overview of the SWOT analysis**

4 The Dutch innovation ecosystem for nuclear medicine in international perspective

4.1 Actors in the innovation ecosystem for nuclear medicine in EU and USA

The Dutch ecosystem for nuclear medicine does not operate in isolation. It is internationally well-connected. The Dutch ecosystem is of course strongest connected to the wider EU ecosystem for nuclear medicine. Connections are directly through EU regulations and directives that apply to the Netherlands and through institutions and organisations such as the EMA – the European Medicines Authority, which is responsible for the authorisation of new medicines on the European market – and the EANM – the association for nuclear medicine professionals in Europe. Similarly, R&D is conducted generally in international cooperation and many supply chains for medical isotopes and radiopharmaceuticals are European if not international.

The nuclear medicine ecosystem in the USA is a bit more detached from the Dutch ecosystem, but can provide relevant insights for improving the Dutch ecosystem. Here different regulations apply, and different organisations are active. Several stakeholders have indicated in a short survey that the USA has a stronger innovation ecosystem for nuclear medicine then the Netherlands. The USA is therefore an interesting case to study and – potentially – learn from.

4.1.1 Overview of EU innovation ecosystem actors

4.1.1.1 Government and regulators

Various regulations that apply to the Netherlands and that regulate the approval and use of nuclear medicine in Europe are established by the European Commission and approved by the European Parliament and European Council before they enter into force. Apart from regulations – that apply to the whole of the EU directly – also directives exist. These need to be implemented in national regulation and therefore specific regulations and processes at national level may differ between Member States.

Across the EU several agencies are involved in the regulation and supervision of these regulations regarding medicines and radiation protection. These can be at national level, especially when it concerns directives, or at European level. Within the ecosystem for nuclear medicine these are:

- **European Medical Agency** (EMA), responsible for the centralisation and harmonisation of scientific assessments, marketing authorisation, and supervision of radiopharmaceuticals throughout the EU[100].

100 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
Source: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20190726

- **National Competent Authorities**, agencies at national level throughout the EU that primarily authorise medicines that are not centralised at EMA level. The agencies also serve as a scientific network that supplies access to European experts that work in various committees, working parties or assessment teams to support each member state[101].
- **National regulators for radiation protection and nuclear safety**, these are authorities at national level throughout the EU that authorise the (safe) use of ionising radiation and thus the use of radiopharmaceuticals and working with radioactive materials. In each Member State regulators are differently organised, with responsibilities being spread over multiple organisations, at the ministry or at a separate agency. They provide licenses and oversee whether license holders abide to the rules and regulations regarding radiation protection and nuclear safety. At EU level, the radiation safety authorities collaborate and share knowledge in the HERCA association.

Euratom, or the European Atomic Energy Community (EAEC), is a European international organisation to promote the peaceful use of nuclear energy, but also more widely is concerned with the use of ionising radiation and radiation protection. Euratom is distinct from the EU, but has tight connections (all EU Member States are also automatically a member of Euratom) and was already established before the European Union. Under Euratom directives can be established, such as for radiation protection (for example the BSS Directive), in alignment with international principals of the IAEA. The activities under Euratom are implemented by:

- **Euratom Supply Agency** (ESA), an independent agency under the Euratom Treaty, is a regulatory agency and advisory committee on the equitable supply of nuclear materials throughout the EU. ESA's objective is to secure the supply of nuclear materials and serve as a link between producers and users within the nuclear industry and supporting services[102]. As part of this task, the ESA also takes actions to secure the supply of medical radioisotopes and their source materials and monitors the production chain of medical radioisotopes through the *European Observatory on the Supply of Medical Radioisotopes*.
- **The Joint Research Council** (JRC), the EC's science and knowledge service, originally established under the Euratom Treaty has different locations for research into nuclear technology across the EU. These have some links with the development of new medical isotopes, as for example the HFR in Petten is formally owned by the EC-JRC and the JRC in Karlsruhe supplies some medical isotopes for research purposes (e.g. Actinium-225)[103].

At national level, various ministries of the EU's Member States are concerned with policies that relate to the innovation ecosystem for nuclear medicine. These can be ministries of health that determine national health policies, ministries of science and education whose policies may influence the research, R&D and skills in the ecosystem, and ministries of economy and trade whose policies may influence R&D and the financial climate in the ecosystem.

101 EMA (n.d.). National Competent authorities.
Source: https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human
102 Euratom Supply Agency, European Commission,
Source: https://euratom-supply.ec.europa.eu/about-esa/governance/advisory-committee_en
103 Technopolis Group (2021). Study on sustainable and resilient supply of medical radioisotopes in the EU: Therapeutic Radionuclides. JRC.

4.1.1.2 *Industry: development and production*

Compared to other industries, the nuclear medicine industry is a rather small industry in Europe. Nevertheless, quite a number of companies across the EU are active in the European innovation ecosystem for nuclear medicine. The market is not much consolidated and exists of various players in different stages of the development process (or value chain).[104] In describing the industry in the ecosystem for nuclear medicine in Europe we focus on companies that are active in the nuclear domain and not so much in the wider chemical and biological domain, as this would broaden the scope of the ecosystem significantly. This means that companies should be clearly involved in nuclear medicine and not be, for example, a more generic supplier of biological or chemical input materials.

Across the EU the industry in the innovation ecosystem for nuclear medicine is represented by Nuclear Medicines Europe. In this industry association specialised pharmaceutical companies, producers and processors of medical radioisotopes and equipment providers are represented.

Enrichment and target fabrication

Europe has just two companies that are involved in the enrichment of stable isotopes that are used to produce medical radioisotopes (API in radiopharmaceuticals). These are Urenco and Orano. Stable isotopes are used in targets to produce some of the medical radioisotopes used in nuclear medicine. Such targets are needed in research reactors or cyclotrons.The production of targets (and research reactor fuel) is done by CERCA (Framatome).

Companies in EU	Country
Urenco	*Netherlands*
Orano	France
CERCA (Framatome)	France

Table 5 Identified industrial actors in enrichment and target fabrication in EU nuclear medicine ecosystem

Medical radioisotope production and processing

The production of medical radioisotopes is conducted by a larger variety of actors. In Europe, medical isotopes are mainly produced in nuclear research reactors and cyclotrons. A great many of cyclotrons to produce medical radioisotopes are installed across the EU. About 240 cyclotrons are operational[105], which means that over hundred organisations, including hospitals, must be involved in the production of medical isotopes, primarily for imaging using PET and SPECT.[106]

104 See: https://www.mordorintelligence.com/industry-reports/europe-nuclear-medicine-market
105 NucAdvisor (2021). Co-ordinated Approach to the Development and Supply of Radionuclides in the EU. European Commission.
106 Technopolis Group (2022). Medical isotope production using local cyclotrons. A comparative study between Denmark and the Netherlands. Dutch Ministry of Health, Welfare and Sport.

The number of research reactors producing medical isotopes is significantly smaller, currently seven research reactors are operational. These are operated by NRG (HRF, the Netherlands), SCK-CEN (BR2, Belgium), POLATOM (MARIA, Poland), TUM (FRMII, Germany), CVŘ Řež (LVR-15, Czech Republic), Institute Laue-Langevin (ILL, France) and BNC/AEKI (BRR, Hungary).[107] NRG, SCK-CEN and POLATOM are among the largest suppliers of medical radionuclides for both diagnostic and therapeutic use.

The organisations involved in producing medical radioisotopes are spread across Europe. Table 5 provides an overview of some key industrial actors in the production and processing of medial radioisotopes. This overview excludes the many cyclotron operators across the EU. The table shows that most of these companies are in Germany, France, and the Netherlands.

Companies in EU	Country
TUM	Germany
Eckert & Zeigler	Germany
JRC Karlsruhe	Germany
OranoMed	France
Arronax	France
Institute Laue-Langevin	France
NRG	*Netherlands*
SHINE	*Netherlands*
AlfaRim (start-up)	*Netherlands*
SCK-CEN	Belgium
IRE	Belgium
Polatom	Poland
CVŘ/NPI Řež	Czech Republic
BNC/AEKI/IZOTOP	Hungary
IFE	Norway (NB: not EU)

Table 6 Identified industrial actors in production and processing in EU nuclear medicine ecosystem

107 Technopolis Group (2021). Study on the sustainable and resilient supply of medical radioisotopes in the EU. Therapeutic Radionuclides. JRC.

Pharmaceutical companies

Quite some pharmaceutical companies have ventured into radiopharmaceuticals in recent years. Opportunities in this field have led to acquisitions and new players entering the field (both start-ups and existing companies). Many of the larger pharmaceutical companies operate internationally and have a subsidiary in Europe. Among the larger players in this field are AAA/Novartis (incl. IDB Holland), Bayer Healthcare, Curium Pharma, GE Healthcare, IBA and Boston Scientific.

Table 7 provides an overview of pharmaceutical companies in Europe operating within the innovation ecosystem for nuclear medicine. This list is not complete but contains companies that are mentioned in various sources.[108] Based on these sources, it seems that Germany, the Netherlands, and Belgium are countries with quite some presence of radiopharmaceutical companies.

Companies in the EU	Country
CIS Bio/Revvity	Germany
Sirtex Medical	Germany
Ariceum Therapeutics	Germany
ROTOP	Germany
ITM	Germany
Bayer Healthcare Pharmaceuticals	Germany/Norway
Boston Scientific	*Germany, Netherlands, and other EU countries*
Quirem Medical/Terumo Europe	*Netherlands*
Curium Pharma	*Netherlands and other EU MS*
GE Healthcare	*Netherlands and other EU MS*
AAA/IDB Holland/Novartis	*Netherlands and other EU MS*
IBA	Belgium
PanTera	Belgium
NUCLEIS Radiopharmaceuticals	Belgium
Telix	Belgium
IZOTOP	Hungary
MRP	Hungary
ACOM	Italy
Bracco	Italy

108 Mapping made for the study referenced in footnote 107, website of NMEU,

Companies in the EU	Country
OranoMed	France
MGP	Czech Republic
Blue Earth Diagnostics	Ireland/UK
Nordic Nanovector/Thor Medical	Norway

Table 7 Identified industrial pharmaceutical companies active in the EU nuclear medicine ecosystem

4.1.1.3 Research organisations

Research in nuclear medicine is conducted along the value chain. This includes research centres, universities and academic hospitals, pharmaceutical companies and producers of medical isotopes and tracers. Various of these organisations have been identified under the headings industry, intermediary organisation, hospitals, and pharmacies. Here, we refer to research organisations as organisations that have as their main goal to conduct scientific research, be it fundamental, experimental, or translational.

The SCImago Institutions Ranking has ranked 783 research institutions in Europe, of which 627 organisations in an EU Member State, within the domain of 'Radiology, Nuclear Medicine and Imaging' in 2023.[109] Although this domain is wider than nuclear medicine per se, it provides an indication of the width of the ecosystem in terms of research organisations, which include medical schools, universities, and academic hospitals. The ranking considers indicators based on research, innovation, and societal impact.[110] The ten highest ranked research organisations are in Germany, France, the UK, and the Netherlands. The first Dutch institution in the ranking is at rank 7 (Utrecht University). In the top-50 and top-100 are resp. 13 and 17 Dutch research institutions ranked. German (26) and Dutch (17) research institutions are highest in number in this top-100 ranking, followed by the UK (14), France (11) and Italy (11). Globally, five US institutions rank higher than the first European research institution in this field.[111]

The SCImago Institutions Ranking shows that many research organisations in Europe are active in the field of nuclear medicine and that the EU is performing well in research in this domain, performing on internal top level. This is also confirmed in interviews, where the picture emerges that the US is slowly losing its leading position in this field to the EU and Australia. Countries of the EU that perform well academically are Germany, France, and the Netherlands. Dutch academic actors in this field have, based on their research activities, a noticeable position within the European ecosystem.

109 SCImago Institutions Ranking (2023): https://www.scimagoir.com/rankings.php?area=2741&ranking=Overall&country=all

110 These indicators are based on bibliometrics (publications and citations in the SCOPUS database), technometrics (references in patents in the PATSTAT dataset) and altmetrics (from data on social media, Mendeley, Google and the ahrefs database).

111 Based on Global ranking and selection for European countries.

At the EU level, the JRC, ESA/EC DG Energy and EC DG RTD fund research and training related to nuclear medicine. The JRC also conducts research on its sites that are related to medical radioisotopes. The Euratom Research and Training Programme, the Health cluster of Horizon Europe and EU4Health Programme provide funding for research related to nuclear medicine. The EURAMED project, conducted under the SAMIRA Action Plan – which also addresses actions related to nuclear medicine – has resulted in a European Research Roadmap for medical applications of ionising radiation for better and individualised healthcare to improve patients 'lives. In this roadmap eight breakthroughs are defined, including improving/developing diagnosis and therapy (incl. theragnostics and interventional procedures) in nuclear medicine. This shows that the EU is taking actions to improve nuclear medicine in Europe through research and innovation and that the nuclear medicine community in Europe is seeking coordination in setting EU wide challenges, goals, and actions.

4.1.1.4 Intermediary organisations

Intermediary organisations in Europe include organisations that support in clinical trials and organisations that represent any of the actors in the ecosystem, such as sector associations. These organisations act as intermediaries between research and industry, research and government and industry and government.

A complete overview of CROs that support development and in clinical trials for nuclear medicine could not be produced within the scope of this study. There seem to be however a few CROs that have some sort of specialisation in nuclear medicine or experience with clinical testing of radiopharmaceuticals in Europe. We have identified four of these CROs, including two in the Netherlands (Tracer CRO and ICON). One of the largest specialised CROs in the field of nuclear medicine seems to be ABX-CRO in Germany and PSI CRO in Switzerland.

Organisations that represent key actors in the ecosystem exist at national and European level. Most EU countries do have a national association for nuclear medicine. At EU level the European Association for Nuclear Medicine (EANM) represents nuclear medicine professionals. This association is also active in research projects and provides input to legislation. It is a recognised stakeholder by the European Commission and has several working groups working collaboratively on issues shared by its members. Other associations relevant in nuclear medicine are Nuclear Medicine Europe (NMEU), who represents the key industrial actors in the nuclear medicine sector (incl. producers, pharmaceutical companies, and suppliers/equipment manufacturers). These are the tow key associations in nuclear medicine. However, there are also separate associations for Medical Physics Experts (EFOMP) and radiochemistry (EuChemS – Division of Nuclear and Radiochemistry).

Companies in the EU	Type	Country
ABX-CRO	CRO	Germany
PSI CRO	CRO	Switzerland (non-EU)
Aixial Group	CRO	France (HQ), Belgium, Czech Republic, Denmark, Romania, Sweden
TRACER	CRO	Netherlands
ICON	CRO	Netherlands and many other EU countries
EANM	Association	Austria
NMEU	Association	Belgium

Table 8 Identified intermediary organisations active in the EU nuclear medicine ecosystem

4.1.1.5 Hospitals and pharmacies

Throughout Europe there are many hospitals and pharmacies involved in nuclear medicine. Many hospitals have a nuclear medicine department. Based on data from previous publications, somewhere between 766[112] and 802[113] medical centres in the EU provide radionuclide therapy to their patients. Most of these hospitals do have some radiopharmacy support in-house.

However not all hospitals have the right facilities to offer all diagnostic and therapeutic treatments in nuclear medicine, existing data suggests that this is often the case in less than half of the medical centres (although for many EU member states this difference is not known). Facilities required for radiopharmaceutical therapy require significant investments and are therefore mainly in the larger and/or academic hospitals and not in smaller peripheral hospitals.[114] These hospitals have also a more extensive radiopharmacy.

4.1.1.6 Patients

At member state level and at EU level various patient organisations exist that represent patients that could benefit from nuclear medicine. There are organised across medical disciplines or by diseases. We therefore have not included an overview of patient organisations. As however many nuclear medicine applications are used in the treatment of cancer, at EU level an important patient organisation is European Cancer Patient Coalition (EU and non-EU).

112 Based on Technopolis Group (2021). Study on the sustainable and resilient supply of medical radioisotopes in the EU. Therapeutic Radionuclides. JRC. Data not validated for all EU member states.
113 Based on Gleisner, K. S., Spezi, E., Solny, P., et al. (2017). Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey. EJNMMI physics, 4(1), 28. Data not complete for all EU member states.
114 Technopolis Group (2021). Study on the sustainable and resilient supply of medical radioisotopes in the EU. Therapeutic Radionuclides. JRC.

4.1.2 Overview of US innovation ecosystem actors

4.1.2.1 Government and regulators

The USA has a relatively simple regulatory framework for radiopharmaceuticals compared to the EU. Most regulations and oversight are organised at federal level, but the oversight for devices used to administer radiopharmaceuticals is organised at State level. Nuclear medicine is regulated in the United States primarily by two federal administrations. These are:

- **the U.S Food and Drug Administration** (FDA), the government regulatory agency responsible for ensuring the safety and efficacy of radiopharmaceuticals[115]. The FDA regulates the access of pharmaceuticals to the market in all States.
- **the Nuclear Regulatory Commission** (NRC), an independent agency that regulates the use of nuclear materials and oversees the conditions of facilities ensuring the security and safety in the production of radiopharmaceuticals[116]. The NRC regulates at federal level and in thirteen States that don't have their own programme for the regulation of radioactive materials. The other States need to have regulation that is at least as stringent as the NRC and need to organise their own oversight.[117] The NRC receives advise on the needs of the nuclear medicine community from the *Advisory Committee on The Medical Use of Isotopes (ACMUI)*, a committee providing recommendations to the NRC on the production and processing of radioisotopes. This input supports the creation of the regulatory framework for medical applications[118].

In addition to the above, the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA) and the Department of Transportation (DOT) are involved in the oversight of the production, transport and working with nuclear medicine.[119] Within DOT the *Pipeline and Hazardous Materials Safety Administration (PHMSA)* is a governmental agency overseeing the safe of transportation of hazardous materials in the production of radiopharmaceuticals[120].

The US government has little funding and policies to support R&D in nuclear medicine. Available government funding is highly competitive with low success rates. Clinical studies are conducted with funding from foundations or from industry, and sometimes covered by revenues from the hospital – which operate more commercially than in the Netherlands.

4.1.2.2 Industry: development and production

Enrichment and target fabrication

The USA has only few domestic enrichment facilities for the enrichment of isotopes.[121] The main enrichment facility is used for the enrichment of uranium; this is done in New Mexico by Urenco USA (a Dutch-British-German multinational). Centrus Energy Corp[122] is also constructing

115 U.S. Food & Drug Administration, Source: https://www.fda.gov
116 Nuclear Regulatory Commission, Source: https://www.nrc.gov/about-nrc.html
117 Oklahoma City University (n.d.). Nuclear Medicine: Introduction to U.S. & International Regulations and Clinical Practice Resources: U.S. Regulations. Chickasaw Nation Law Library: https://libguides.okcu.edu/c.php?g=225265&p=1492829
118 Advisory Committee on the Medical use of Isotopes, U.S. Nuclear Regulatory Commission, Source: https://www.nrc.gov/about-nrc/regulatory/advisory/acmui.html
119 Dao Le (2020). An Overview of the Regulations of Radiopharmaceuticals. In: Locoregional Radionuclide Cancer Therapy, Springer, pp 225-247.
120 Pipeline and Hazardous Materials Safety Adminstration, Source: https://www.phmsa.dot.gov
121 US NRC (n.d). Available at: https://www.nrc.gov/info-finder/materials/index.html
122 Centrus Energy (n.d.). Available at: https://www.centrusenergy.com/who-we-are/

a uranium enrichment facility in the USA but is not yet operational. Only in the Netherlands, Urenco produces stables isotopes required to produce medical radioisotopes. In the USA, the ORNL Enriched Stable Isotope Pilot Plant (ESIPP) produces small quantities of stable isotopes. This pilot plant should in the future be expanded into the US Stable Isotope Production and research Facility (SIPRC).[123]

The US DOE Isotope Programme is working with various research facilities and national laboratories to produce some stable isotopes for domestic supply, primarily for research purposes. Only under strict criteria domestic organisations can obtain stable isotopes through the US DOE. To this end the US DOE has launched the National Isotope Development Center.[124]

Targets (or research reactor fuel) are manufactured mainly for energy purposes (e.g. uranium targets), by a few suppliers such as BWX Technologies, Framatome (a French multinational).[125] We could not identify US suppliers of targets for specifically medical applications and targets other than uranium targets.

Medical radioisotope production and processing

The production of medical isotopes in the USA encompasses a wide range of actors, most of them at research institutions and hospitals. These include nuclear research reactors and cyclotron facilities. The USA hosts a substantial number of cyclotron facilities spread across various research institutions, hospitals, and private enterprises, such as the Cardinal Health Cyclotron Facilities, the University of Washington Medical Cyclotron Facility, and the University of Pittsburgh PET Facility in collaboration with Siemens[126],[127]. Research reactors, operated by institutions such as Oak Ridge National Laboratory[128] and the University of Missouri Research Reactor Center[129], contribute to producing medical isotopes for diagnostic and therapeutic purposes in the USA. The USA has no large scale commercial medical radioisotope production such as in the HFR in Netherlands. The USA therefore needs to import some of its medical radioisotopes overseas. SHINE (also based in the Netherlands) is one of the few commercial suppliers in the USA that started operation in recent years, focusing on the production of lutetium-177 and molybdenum-99.[130]

While the USA has production capabilities for medical isotopes, there have been concerns about the supply chain and dependence on foreign sources for critical radioisotopes. To secure and increase the domestic supply of medical radioisotopes, several efforts have been made to address these issues. The American Medical Isotopes Act of 2012 initiated the improvement of the reliability of domestic isotopes through initiatives. The Act set out to

123 NIDC (n.d.). Available at: https://www.isotopes.gov/other-facilities
124 NIDC (n.d.). Available at: https://www.isotopes.gov/production-network
125 US NRC (n.d.). Available at: https://www.nrc.gov/info-finder/materials/index.html
126 Cyclotrons used for Radionuclide Production, Database of Cyclotrons for Radionuclide Production, (2024). IAEA- Accelerator Knowledge Portal. Available at: https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx
127 UW Medicine- Department of Radiation oncology, (n.d.). Available at: https://radiationoncology.uw.edu/research/cyclotron/
128 Oak Ridge National Laboratory (n.d.). Available at: https://www.ornl.gov/?gclid=CjwKCAiAq4KuBhA6EiwArMAw1Bz2guu25EYEo7WO-ZAkn4eMSgSklrXSSde-E5KeOXWPc1t7r9-aBoCBc4QAvD_BwE
129 Research Reactor, University of Missouri (2024). Available at: https://www.murr.missouri.edu
130 SHINE (n.d.) Available at: https://www.shinefusion.com/phase-2

evaluate and support medical isotope production projects within the USA[131]. These supported initiatives include the US DOE Isotope Program, hosted by Oak Ridge National Laboratory, and funded by the US DOE Isotope R&D and Production Program. The purpose of the program is to produce and distribute radioisotopes that are in short and critical need of supply. The program supports isotope production, new production techniques, workforce development and reducing dependency on international supply chains. The efforts of the US DOE Isotope Program strive to increase the profitability and the security of supply of medical isotopes in the USA[132] Other efforts, such as those undertaken by companies like US Nuclear (UCLE) and Fusion Power Corporation also aim to address the shortage of medical radioisotopes through clean fusion power[133],[134]. Based on these efforts, as of 2022, The FDA's Center for Drug Evaluation and Research (CDER) and the US DOE National Nuclear Security Administration (DOE/NNSA) identified that the USA has reached sufficient supply of molybdenum-99 – a widely used medical radioisotope used in diagnostics with SPECT[135].

Pharmaceutical companies

Many pharmaceutical companies that are based in the USA offer radiopharmaceuticals. Large US-based pharmaceutical companies in this area include Novartis and Bayer[136]. The companies vary based on their radiopharmaceutical portfolio and infrastructure. They provide several (therapeutic) radiopharmaceuticals including theranostics[137]. The companies collaborate with research institutions to continuously develop innovative products. For instance, Bayer collaborated with the Oak Ridge National Laboratory to develop medical radioisotopes for treatment of prostate cancer[138]. Additionally, there is a growing trend of new radiopharmaceutical companies emerging, indicating an active and expanding market in this sector[139]. The USA serves as a crucial market for clinical trials, especially for cancer treatments conducted by pharmaceutical companies, further highlighting its significance in the field of radiopharmaceutical development[140].

131 The American Medical Isotope Production Act of 2012, Molybdenum -99 for Medical Imaging, (2016). Committee on State of Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium; Nuclear and Radiation Studies Board; Division on Earth and Life Studies; National Academies of Sciences, Engineering, and Medicine: National Academic Press. Available at: https://www.ncbi.nlm.nih.gov/books/NBK396175/

132 Isotope Science and Engineering Directorate, (n.d.). Oak Ridge National Laboratory. Available at: https://www.ornl.gov/content/doe-ip-production-site#:~:text=The%20DOE%20Isotope%20Program%20supports,the%20National%20Isotope%20Development%20Center

133 "Medical Radioisotopes", (2024). US Nuclear Corp. Available at: https://usnuclearcorp.com/?s=medical+radioisotopes

134 Technology- Principles of Fusion Energy Generation, (2011). Fusion Power Corporation. Available at: https://www.fusionpowercorporation.com/technology/

135 From our perspective: FDA's Role in Helping a Critical Medical Isotope meet sufficient supply in the US for the first time, (2022). U.S. Food and Drug Administration. Available at: https://www.fda.gov/drugs/our-perspective/our-perspective-fdas-role-helping-critical-medical-isotope-meet-sufficient-supply-us-first-time

136 Top 20 Radiopharma companies based on Market Cap, (2023). PharmaShots. Available at: https://www.pharmashots.com/14882/top-20-radiopharma-companies-based-on-market-cap

137 61 Radiopharmaceuticals Companies, (2024). Certara. Available at: https://biopharmguy.com/links/company-by-location-radiopharmaceuticals.php

138 ORNL ramps up production of key radioisotope for cancer-fighting drug, (2018). Oak Ridge National Laboratory. Available at: https://www.ornl.gov/news/ornl-ramps-production-key-radioisotope-cancer-fighting-drug

139 Going nuclear: radiopharmaceuticals see surge in funding, (2023). Labiotech. Available at: https://www.labiotech.eu/in-depth/radiopharmaceutical-market-funding-surge/

140 Fox Chase Cancer Center Invests in Expanding Access to Lifesaving Radiopharmaceuticals for Cancer Patients, (2023). Fox Chase Cancer Center Temple Health. Available at: https://www.foxchase.org/news/2023-10-17-fox-chase-cancer-center-invests-in-expanding-access-to-lifesaving-radiopharmaceuticals-for-cancer-patients

4.1.2.3 *Research organisations*

The United States is strong in research in the field of 'Radiology, Nuclear Medicine and Imaging'. The worldwide top-50 of the SCImago Institutions Ranking is dominated by US research organisations. the first five institutions are all from the USA: (1) Harvard University, (2) Harvard Medical School, (3) Massachusetts General Hospital, (4) Mayo Clinic and (5) The John Hopkins University.[141]

The USA is also leading in terms of clinical trials.[142] Most pharmaceutical companies first target the US market and therefore also naturally look for clinical trials in the USA. This results automatically in more research activity from pharmaceutical companies across the globe in the US. Where Europe is strong in early-phase clinical trials, the US is stronger in later trials. These are conducted in collaboration with other hospitals and with pharmaceutical businesses and with involvement of other medical specialties. Oncologists are often leading such clinical trials, as they can provide patients and have more funds available.

Research is also conducted earlier in the value chain for radiopharmaceuticals. The US is particularly active in research regarding the production of medical radioisotopes, emerging from the government's priority to increase domestic production of medical radioisotopes. Innovations in the production of medical radioisotopes, such as the technology of SHINE, have been developed in the US.

4.1.2.4 *Intermediary organisations*

Intermediary organisations are organisations that support in development and clinical trials and organisations that represent any of the actors in the nuclear medicine innovation ecosystem of the USA, such as sector associations. These organisations act as intermediaries between research and industry, research and government and industry and government.

A complete overview of CROs that support in development and clinical trials for nuclear medicine could not be produced within the scope of this study. However, we have identified five CROs that are specialised in supporting clinical studies in nuclear medicine. These are the US companies Medpace and Invicro, and US subsidiaries of the EU-based Tracer CRO, ABX-CRO and Aixial Group.

The most relevant organisations that represent key actors in the ecosystem is the Society for Nuclear Medicine and Molecular Imaging (SNMMI), the US counterpart of the EANM. This association is also involved in government advocacy of nuclear medicine.

4.1.2.5 *Hospitals and pharmacies*

Many hospitals and pharmacies are involved in nuclear medicine in the USA. No full overview could be provided. About 40 hospitals have a cyclotron in the USA, but most rely on commercial providers.

141 SCImago Institutions Ranking (2023): https://www.scimagoir.com/rankings.php?area=2741&ranking=Overall&country=all
142 See the more detailed discussion in section 4.2.

The SNMMI has, based on set criteria for the provision of nuclear medicine therapy, listed 69 medical centres as Radiopharmaceutical Therapy Centers of Excellence.[143] These medical centers offer radiopharmaceutical therapy to patients. Of these, 20 are designated as clinical centers of excellence, meaning that they have experience with multiple nuclear medicine therapies. In total 36 medical centres are designated as comprehensive centers of excellence, as these centers are considered to lead the growth of the field of radiopharmaceutical therapy.

4.1.2.6 Patients

The USA has various patient organisations that represent patients that benefit from nuclear medicine. Most of these organisations are organised across medical disciplines or by diseases. We therefore have not included an overview of patient organisations. As however many nuclear medicine applications are used in the treatment of cancer, two key patient organisations are highlighted. One of the biggest and perhaps most relevant patient organisation for nuclear medicine in the USA is the American Cancer Society. The more focused Prostate Cancer Foundation has been supporting research into radiopharmaceuticals targeting PSMA.

4.2 Position of the Netherlands in the international landscape

The Netherlands has a noticeable position in the international nuclear medicine sector. Both in terms of innovation as well as production the Netherlands has international visibility. This is indicated by:

- The fact that 13 Dutch research institutions are ranked in the top-50 of the SCImago Institutions Ranking for the field of 'Radiology, Nuclear Medicine and Imaging' in 2023.[144] In addition, the Netherlands is scoring well in terms of highly cited papers in this field in the last decade[145] (see Figure 13-A) and in terms of research output (i.e. research activity or productivity) – being ranked 9th internationally in terms of the number of publications in the field of "Radiology, Nuclear medicine and Medical Imaging" over the period of 1986-2010[146]. This position is confirmed by several interviewees who state that Dutch research in the field of nuclear medicine is internationally recognised and of high quality.
- Consulted multinationals and professionals that moved to the Netherlands in the field of nuclear medicine, indicate that the quality of the research, the highly skilled professionals, the good infrastructure, and the density of hospitals in this field make the Netherlands an interesting country for businesses and professionals.
- Since the early 2000s, four Dutch professors have been the president of the EANM (out of the 11 presidents during that period)[147], giving a clear Dutch presence in Europe. In addition, the Dutch government and sector have made various efforts to put the topic of medical isotopes on the European and international agenda, for instance with its special envoy for medical isotopes in 2021[148].

143 SNMMI, Source: https://sites.snmmi.org/Therapy/SNMMI-THERAPY/Radiopharmaceutical_Therapy_Centers_of_Excellence.aspx
144 SCImago Institutions Ranking (2023): https://www.scimagoir.com/rankings.php?area=2741&ranking=Overall&country=all
145 Yan S, Zhang H, Wang J. (2022). Trends and hot topics in radiology, nuclear medicine and medical imaging from 2011-2021: a bibliometric analysis of highly cited papers. Jpn J Radiol. 40(8):847-856.
146 Y.J. Ku et al. (2012). Korea's Contribution to Radiological Research Included in Science Citation Index Expanded, 1986-2010. Korean J. Radiol. 2012, 13(5), 523-529.
147 See for an overview over past presidents of the EANM: https://www.eanm.org/about/organs/past-presidents/
148 VWS (2021). Eerste bevindingen speciaal gezant medische isotopen: https://open.overheid.nl/documenten/ronl-30132f88-bb8c-4a34-83ec-7f4f72a5660d/pdf

- The current HFR research reactor in Petten is an important international producer and supplier of medical radioisotopes and well-known internationally. The conception of the PALLAS reactor has drawn international attention to the Netherlands and ensured a future strong position in the medical radioisotope market. Investments of SHINE and Novartis in production facilities in the Netherlands have further strengthened this international position and visibility.

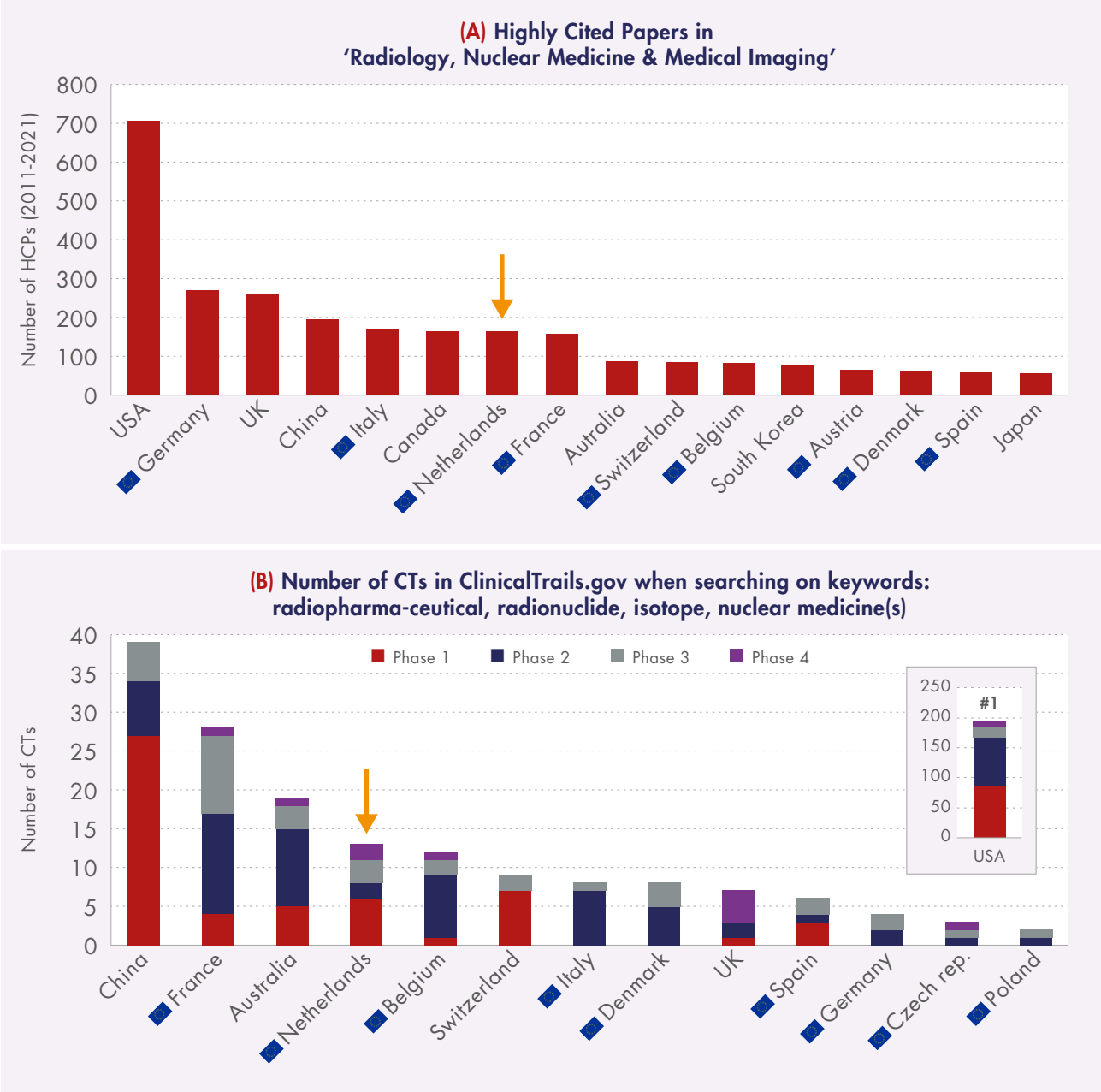

Figure 13 **The position of the Netherlands compared to other countries in terms of (A) highly cited papers and (B) starting and ongoing clinical trials**

Nevertheless, the Netherlands is a small country with a small market for nuclear medicine. Pharmaceutical companies consider the European market as a whole and focus generally first on the US market. Not many clinical trials in this domain are conducted in the Netherlands, currently only 13 starting or ongoing clinical trials related to nuclear medicine are registered in the ClinicalTrials.gov database[149]. This is (far) less than the USA, China, France, and Australia, but higher than many European countries as can be observed in Figure 13-B.

Some other countries do have – in some respects – a stronger innovation ecosystem for nuclear medicine than the Netherlands, according consulted actors in the Dutch ecosystem. Germany, the United States and Australia are most often mentioned in our mini survey as having a stronger innovation ecosystem than the Netherlands. From the EU countries, also Belgium and France have been mentioned by quite a few respondents. The response from the mini survey conducted in this study is presented in Figure 14.

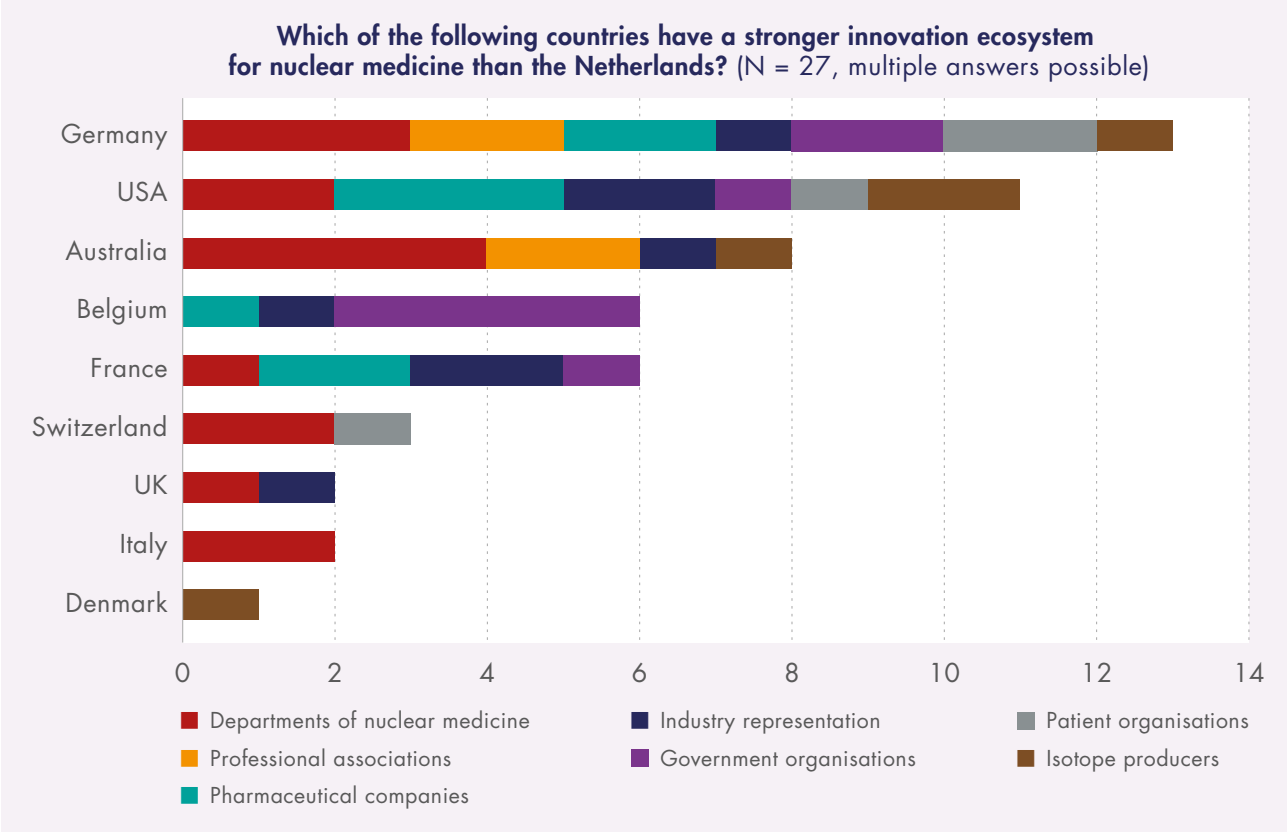

Figure 14 Response from the mini survey regarding strong foreign innovation ecosystems for nuclear medicine

149 These are clinical trials that emerged on 24-01-2024 when querying the ClinicalTrials.gov database on the keywords "isotope OR radionuclide", "radiopharmaceutical" and "nuclear medicine OR nuclear medicines" as an indicator for clinical trial activity in the Netherlands. Status filtered on Active, not recruiting, Available, Enrolled by invitation, Not yet recruiting, Recruiting .

Germany is considered to have a strong innovation ecosystem. Many radiopharmaceuticals are researched in Germany. Germany has a generous compassionate use policy, allowing to treat patients sooner with novel, unauthorised radiopharmaceuticals outside clinical trials. This has led to early access for patients to promising new radiopharmaceuticals and various clinical case studies. However, conducting clinical trials is said to be more complicated (in terms of regulation) than in the Netherlands. R&D in Germany is therefore also hard to scale up. Germany has quite some pharmaceutical companies and production facilities for radiopharmaceuticals (e.g. in Munich). Some respondents also mention that Germany has good research infrastructure, access to finance and strong research institutions.

The **United States** is also considered to have a strong innovation ecosystem. Regulation is in some respects considered more favourable, as respondents indicate that procedures are generally faster and regulatory costs lower. Risk taking is also considered much higher in the USA, with a more entrepreneurial spirit in the ecosystem. In addition, the USA has strong research institutions in the field of nuclear medicine, many clinical trials are conducted in the USA (as it is the key market to launch new pharmaceuticals) and the government is actively strengthening the supply chain for medical radioisotopes. The USA has limited national supply of medial radioisotopes and wants to reduce its international dependency. A weakness of the USA is the shortage of well-trained nuclear physicians. Many nuclear medicine physicians are trained radiologists with a rather short additional training into nuclear medicine. They are not sufficiently trained to provide nuclear medicine therapy, which is an increasing part of the work of nuclear medicine physicians. This concern was voiced in literature[150] and interviews.

The strength of the **Australian innovation ecosystem** for nuclear medicine is its ability to conduct large multicentre studies (prospective clinical trials). Due to government funding, Australia has good infrastructure for nuclear medicine, and thanks to government grants clinical trials have increased. The latter is also due to better organisation of the innovation ecosystem through the Australian Radiopharmaceutical Trials Network (ARTnet)[151] to foster collaboration in and improve processes for multicentre clinical trials across Australia and New Zealand. The regulatory environment is considered favourable, with no requirements for GMP for early-phase investigator initiated clinical trials in public hospitals.[152] Australia also has modern infrastructure to produce medical radioisotopes with the ANSTO-operated OPAL research reactor opened in 2007 and its processing facilities.

150 Michael M. Graham (2023). The Future of Nuclear Medicine in the United States. Journal of Nuclear Medicine, August 2023.122.265314; DOI: https://doi.org/10.2967/jnumed.122.265314

151 See: https://artnet.org.au/

152 Andrew M. Scott and Johannes Czernin (2021). Perspectives on Theranostics and Nuclear Medicine. A Conversation Between Andrew Scott and Johannes Czernin, Journal of Nuclear Medicine November 2021, 62 (11) 1492-1494; DOI: https://doi.org/10.2967/jnumed.121.263243

4.3 Lessons for the Netherlands from foreign innovation ecosystem

Foreign innovation ecosystems provide some lessons or insights that can be useful to improve the Dutch innovation ecosystem. These are:

- **Good organisation improves the innovation ecosystem**. Both at EU level and in Australia the ecosystem is more organised and represented. In the EU this is through various committees and high-level groups with the Commission and the EANM. In Australia this this the strong ARTnet network to foster collaboration and strive for multicentre clinical trials.
- **Clear procedures and less strict regulations are favourable for innovation**. Although hard to change, the generally simpler, faster, and cheaper regulatory system for medicines and nuclear permits in the USA is considered favourable for businesses. Also, in Australia regulation is considered more beneficial in terms of (no/little) GMP restrictions for early-phase investigator led clinical trials. The less restrictive German compassionate use policy is said to have spurred innovation and early use of novel radiopharmaceuticals in Germany.
- **Proper education in nuclear medicine is important to have human capital meet future demand**. Concerns have been raised about the changes in education for nuclear medicine physicians in the USA, leading to a shortage of well-trained nuclear medicine physician. Radiology has been the emphasis in training and has also become a larger part of the combined training in the Netherlands. This is considered a concern due to a shift towards therapy in the field.
- **Investments drive innovation**. In Australia government funding for clinical trials and investments in infrastructure have fostered innovation in nuclear medicine. The more entrepreneurial and risk-taking culture in the USA is said to contribute to investments and new business generation.

5 Conclusions and recommendations to improve innovativeness and earning capacity

This chapter provides the main conclusions from this study, as well as recommended actions to further improve the innovativeness and earning capacity of the innovation ecosystem for nuclear medicine. More information on the relation between findings, conclusions and recommendation can be found in Appendix C.2.

5.1 Main conclusions

5.1.1 Conclusions regarding the innovation ecosystem for nuclear medicine

The Dutch innovation ecosystem for nuclear medicine has great promise but more collaboration and coordination are required to unlock its full potential. Coordination should provide a shared direction and prioritisation of actions to improve the innovation ecosystem for nuclear medicine. Collaboration should improve the process from idea to use of radiopharmaceuticals. This collaboration is multi-faceted:

- Stronger collaboration **between researchers/physicians in nuclear medicine** from different institutions to avoid fragmented R&D activities and to ensure larger/multicentre clinical studies, leading to more impact.
- Stronger collaboration and communication **between research organisations, hospitals, industry, and government** to align (investigator led research) agendas where possible, to identify new and promising innovation directions, to align medical research with medical isotope production (R&D) programmes, to ensure that R&D conducted by academia meets requirements for marketing authorisation by (pharmaceutical) businesses in later stages to foster commercialisation, and to address regulatory, financial, and political factors of the ecosystem.
- Stronger collaboration **with other medical disciplines** (such as oncology, urology, cardiology) and **with patients** to ensure that R&D addresses unmet medical needs, clinical trials are improved and the distance between nuclear medicine and other medical disciplines is reduced, which should contribute to the further involvement of nuclear medicine physicians in treatments and uptake of radiopharmaceuticals in guidelines.

Better collaboration could lead to more high-impact studies and publications, more successful technology transfer (valorisation), more funding from industry and (international) research funders and improved patient care. All in all, it could lead to more efficient use of available funding.

The Dutch innovation ecosystem for nuclear medicine is strong in various respects and known internationally. The completeness of the ecosystem in terms of actors in each stage of the process for development and use of radiopharmaceuticals and for most of the value chain (from enrichment onwards) is unique. Nevertheless, there are opportunities for new actors to enter and strengthen the innovation ecosystem. This can contribute to the innovativeness and the earning capacity of the Netherlands in this domain.

- **Particular strengths of the ecosystem**: completeness in terms of actors, high-quality and sometimes even unique facilities, international connectedness and reputation, and the quality of research.

The innovation ecosystem for nuclear medicine has also some weaknesses. A widely perceived weakness of the Dutch innovation ecosystem for nuclear medicine is in the applicable regulation and shortages in human capital. Many actors feel that the sector is overregulated, that EU Directives are too strictly implemented and that regulatory procedures (at competent authorities) are slow. However, the perceived overregulation arises mostly due to the EU regulatory framework concerning pharmaceuticals and radiation protection applicable to all EU Member States. Ongoing actions at EU level (e.g. by EANM and through the SAMIRA Action Plan) should contribute to resolving some of the regulatory challenges. The improvement of national regulatory procedures requires an open dialogue between competent authorities and the wider actors in the ecosystem for nuclear medicine. Human capital is an actionable concern that both affects industry (e.g. lack of people with radiation protection and radiochemistry educations), academia and hospitals (e.g. quality of education of nuclear medicine physicians) and should be addressed.

- **Particular weaknesses of the ecosystem**: regulation, available funding (for research and valorisation), human capital and education (for radiation protection and nuclear medicine physicians) and taking risk (mainly entrepreneurship and investment).

5.1.2 The process from idea to use of radiopharmaceuticals

The process from idea to use of a nuclear medicine can be improved. The Netherlands is especially strong in research in nuclear medicine and the production of medical radioisotopes. However, the **valorisation of research and the translation into further phases of clinical trials is low**. This is caused by fragmented research activities, small clinical trials and methodologies used, little interaction with other medical disciplines and patients to understand their unmet medical need, and chosen IP strategies. More interaction between disciplines, researchers, and industry, together with improved knowledge about valorisation and translation, could improve this.

Most challenges are experienced during clinical trials. Upscaling of clinical trials into phase III has been very challenging due to required investments, collaboration, involvement of (other) hospitals, sufficient availability of the required medical radioisotope and knowledge about the translational process.

Market access is also considered a barrier in the Netherlands. This is perhaps not specific to nuclear medicine, but exists for many medicines, especially for those that end up in the 'sluis' of VWS. Factors that hamper the process of market access (reimbursed care) in the Netherlands are a **lack of Dutch HTAs and national clinical data required for reimbursement of radiopharmaceuticals that are expensive**. HTAs for radiopharmaceuticals are complicated to conduct well and not conducted often or not timely (prior to market authorisation), in part due to limited expertise in HTAs in the Netherlands. HTAs are also important in communicating the value of nuclear medicine to other stakeholders, such as policy makers, patient organisations and investors. Regarding market access, various consulted actors in the ecosystem have also

mentioned that **stricter Dutch regulation**, for instance regarding medical-ethical committees (for clinical research) and clinical benefit (for reimbursement), are factors that reduce the speed of innovation and market access.

5.1.3 Conclusions regarding the international position of the Dutch ecosystem

The Netherlands has internationally a strong reputation in nuclear medicine and has a strong position in the value chain for nuclear medicine, especially in the production of medical radioisotopes. In various respects **the Netherlands is at the forefront in Europe**, in terms of research, policy discussions, and infrastructure.

The Netherlands holds a recognised position in the EU innovation ecosystem for nuclear medicine. The Dutch are well represented in institutions such as the EANM and NMEU, and active in EU policy discussions. Although the Netherlands is part of the EU ecosystem, and many differences exist between EU Member States, some lessons can be learned at EU level. Most importantly, **the EU ecosystem seems better organised at a high level**. Actors in the European ecosystems meet in associations that are recognised by the EC or in steering groups and high-level groups established under the SAMIRA action plan which allows for coordination in policy, regulation, and other factors that strengthen the EU ecosystem take place, together with dialogue between different actors in the ecosystem. This kind of coordination, open dialogue and collaboration is not structurally embedded in the Dutch innovation ecosystem for nuclear medicine.

5.2 Key recommendations

Before sharing our recommendations, we want to stress that the timing for action is now. There seems to be a **window of opportunity** in which momentum and urgency meet:

- **Momentum**:
  - the Netherlands can capitalise on recent public and private investments in new facilities in the Dutch ecosystem, including PALLAS, SHINE, FIELD-LAB, and Novartis/AAA.
  - the Dutch government and the European Commission are currently actively supporting developments in this sector with their policies and actions, for example through the works of the Dutch 'quartermaster' (in Dutch: kwartiermaker) for medical isotopes, the SAMIRA action plan, and the wider goal of being less dependent on foreign regions.

- **Urgency**:
  - the field and role of nuclear medicine is internationally changing with the development and market entry of new medicines and therapies. This provides potential for the availability of better therapies in the Netherlands. Such changes require action to ensure a frontrunners position for the Netherlands is maintained, especially in R&D – as much R&D is ongoing in other regions (esp. Australia and USA) backed by investments in infrastructure. This requires investments in the innovation ecosystem and in infrastructure in the Netherlands.
  - the opportunity to obtain funding from the National Growth Fund for investments that strengthen innovativeness and/or contribute to the earning capacity of the nuclear medicine ecosystem is likely limited as the NGF is scheduled to end in 2025 and changes may be realised by a new Cabinet.

The recommendations proposed in the following sections should be addressed primarily by FAST in collaboration with the 'quartermaster' for medical isotopes and DECISIVE. These recommendations could be integrated in the process of the 'quartermaster' and within – or in alignment with – any National Growth Fund proposals of the DECISIVE consortium.

5.2.1 Recommendations to improve innovativeness

- Our primary recommendation is to **organise the innovation ecosystem for nuclear medicine by creating a platform** in which academia, hospitals, industry, government, and patient organisations meet to collaborate to i) address challenges in the ecosystem, ii) prioritise actions to strengthen the ecosystem and iii) streamline R&D. Such a platform could take the form of a consortium of public and private partners agreeing to the goals of the consortium, its programme/activities and contributing to its costs. This is usually organised in a consortium agreement. A simple governance with a figurehead, board, advisory board, and organisational support could be sufficient. Examples of platforms of this kind can be found with NGF consortia, or with (much) larger consortia such as the TKI's under the Dutch Topsector policy (e.g. TKI Life Sciences and Health: Health ~Holland) and European Technology Platforms (ETPs). The platform could also take the form of a FAST Hub, such as the platform "Medicijn voor de Maatschappij".[153] Inspiration can also be taken from the Australian ARTnet network.

The following recommendations are related to our primary recommendation, as each is linked to the recommended platform.

- We advise to **complement the platform with a network of a few innovation centres for nuclear medicine across the Netherlands**. Innovation centres have facilities and expertise to conduct collaborative R&D at the forefront of nuclear medicine development and/or to provide novel radiopharmaceuticals to patients. R&D in nuclear medicine requires expensive investments in equipment and facilities. Such investments can best be pooled in a few distributed innovation centres in which a network of hospitals collaborate with academia and industry to conduct R&D in nuclear medicine. This also provides the focus and mass to strengthen the international position of the Netherlands in the nuclear medicine field. Therefore, not too many innovation centres should be created. The Netherlands could have place for at least two, perhaps maximum four of such innovation centres, depending on costs, specialisation of each centre and already realised infrastructure. These innovation centres could take different forms:
  - They could be **in or near an (academic) hospital** providing excellent, shared facilities for the clinical testing of novel radiopharmaceuticals and for providing more complex nuclear medicine therapies that require high demands in terms of infrastructure (for waste, radiochemistry/radiopharmacy and cyclotron-production). Such an innovation centre could be a European lighthouse for R&D and education of nuclear medicine physicians. Academic hospitals with already excellent clinical infrastructure for these activities would be well placed for such an innovation centre.

153 See: https://medicijnvoordemaatschappij.nl/

- They could be **at sites where medical radioisotopes are produced**, focusing on R&D in novel medical radioisotopes and novel radiopharmaceuticals (radiopharmaceuticals) that can be used in clinical trials at hospitals. Infrastructure could be accessible for start-ups and new businesses as well, as they cannot afford such infrastructure, but may contribute to earning capacity. The FIELD-LAB is already offering most of this and could be one of these innovation centres.
- They could be located at **already existing hotspots for nuclear medicine** (see section 3.1.1) in the innovation ecosystem to further strengthen such hotspots and to make it **interesting for new businesses to be located** near such a hotspot.

The recommended platform could provide a forum for stakeholders to come together to discuss the practical implementation of these innovation centres, to address any issues around access, timing and duration of a wait period, location, or other factors to ensure these centres sufficiently respond to the ecosystem's needs. Inspiration and lessons could be taken from the PharmaNL project that was previously funded by the National Growth Fund and that aims to build shared infrastructure for the development, upscaling, and production of innovative medicines in the Netherlands.[154]

- **Focus/coordinate investigator-led R&D activities and actions by developing a shared roadmap** with this platform. This roadmap should set shared goals and priorities for Dutch investigator-led R&D in nuclear medicine based on unmet medical needs. The role of the innovation centres should also be addressed in this roadmap if stakeholders wish to pursue the introduction of these centres. Producers could be part of this roadmap to align small-scale production of novel medical radioisotopes to scheduled R&D. Pharmaceutical companies could support actions in this roadmap, collaborate in selected R&D projects and potentially share knowledge for improved valorisation. Roadmapping is a planning exercise which links goals back to R&D actions to assist in achieving these aims and identifying the roles of different actors in the ecosystem for each of these actions.
  - **Address R&D strengths**. As a starting point for this roadmap, performing a horizon scan of currently ongoing studies and existing expertise in nuclear medicine in the Netherlands could identify what strengths could be exploited in the roadmap.
  - **Address medical needs**. Discuss unmet medical needs that could be addressed with radiopharmaceuticals with relevant medical disciplines and patient organisations to identify starting points for R&D.
  - **Address barriers in the innovation ecosystem**. Define actions to improve the innovation ecosystem for nuclear medicine in the Netherlands in the roadmap. This could include some of the other recommendations in this chapter.

154 See: https://www.pharmanl.org/programmalijn-1-pharmanl-infrastructure/

- **Commit public and private investments to this roadmap**. All actors involved should be committed to the roadmap to make it a success. To strengthen this commitment all involved stakeholders (e.g. industry, research organisations, hospitals, and government) should contribute to funding investments. Some such investments (e.g. in research infrastructure) may require more significant contributions from government to reduce risks and to trigger private investments. The contribution from the Dutch government could be through the National Growth Fund.

- **Use the platform to engage with competent authorities and the ministries to discuss procedural and regulatory barriers** with the aim to reduce those barriers within the scope of existing EU legal frameworks. Change would likely be a long road, so the aim of such discussions should also be to create better mutual understanding. This should include understanding what applicants/the sector can do or what is needed to speed up processes, what support can be offered/is available etc. This should result in being better informed and prepared for such procedures (already in the early phases of research to make this goal oriented) as well as producing (national) evidence that is required in these procedures, such as HTAs. Both the EMA and CBG already provide support to academics to navigate regulation and procedures that could be used.[155]

5.2.2 Recommendations to improve earning capacity

- **Improve the valorisation/translation of R&D in nuclear medicine by organising dedicated valorisation support at the innovation centres**. Knowledge about clinical trial methodology/ strategies, applicable regulation, (pre-competitive) industry collaboration, IP, investments, and business spin-off/start-up generation may be limited to specific R&D actors in nuclear medicine. Further promotion of start-up creation, longer IP strategies (i.e. maintain IP beyond phase II CTs to create more value) and business collaboration can contribute to further uptake of innovations and the economic and societal earning capacity of the ecosystem. To this end, collaboration could be sought with the Deltaplan Valorisatie that was recently funded by the National Growth Fund.[156]

- **Market the Dutch ecosystem for nuclear medicine better in the Netherlands and abroad to attract businesses, talent, and investments.** The Netherlands has a strong innovation ecosystem for nuclear medicine with unique facilities. Further investments in this ecosystem should also be known internationally to attract business, talent, and investments. The Dutch ecosystem for nuclear medicine could be visible as platform in relevant conferences, sharing developments and opportunities in the Netherlands or by joining missions abroad. Such international marketing could be undertaken in collaboration with the Netherlands Foreign Investment Agency (NFIA), the Regional Development Agencies (ROMs) and the Netherlands Enterprise Agency (RVO). Some action has already been taken in this respect.[157]

155 See: https://english.cbg-meb.nl/topics/mah-scientific-and-regulatory-advice and https://www.ema.europa.eu/en/documents/leaflet/ema-tools-available-medicines-developers-academic-sector_en.pdf

156 See: https://www.nationaalgroeifonds.nl/overzicht-lopende-projecten/thema-sleuteltechnologieen-en-valorisatie/deltaplan-valorisatie

157 See the Invest in Holland (NFIA) leaflet titled "The Netherlands. A thriving ecosystem in the field of medical isotopes" in which the regional development agencies OostNL and NHN are involved and the upcoming mission to the UK organized with RVO.

- **Address human capital needs and requirements with (higher) education providers as a platform.** Future demand for human capital should be articulated to these education providers, both in industry (needs for radiochemists, radiation protection officers etc.) as well as in healthcare (needs for radiopharmacists, nuclear medicine physicians, specialised nurses). Concerns raised about the education of nuclear physicians (more oriented towards radiology and diagnostics) vis-à-vis the development of the field into therapeutics (requiring more knowledge of internal medicine) should be addressed with universities. These efforts could be best aligned or combined with actions and investments made for human capital in the wider Dutch nuclear sector supported by the Ministry of Economic Affairs and Climate and within the Dutch Topsector Policy.[158]

- **Strengthen the demand side for nuclear medicine.** The demand for novel radiopharmaceuticals may, in part, be reduced by the uptake in hospitals due to required investments in infrastructure and facilities. Ensuring these therapies can be provided to patients increases the earning capacity from a societal (better healthcare) and economic perspective (if Dutch businesses involved). This should not be done at each hospital, but more centralised, such as in some of the innovation centres located at (academic) hospitals. The recommended innovation centres should contribute to strengthening the demand side.

158 See the letter to Parliament regarding "Voortgang ontwikkelingen nucleaire kennis- en innovatiestructuur" from 20 December 2023 in which is referred to a Human Capital Agenda and the Nuclear Academy to support human capital in the wider nuclear sector.

Appendix

Appendix A
Regulatory frameworks relevant to the development and use of radiopharmaceuticals in the Netherlands, EU, and United States

In this chapter we provide further insights in the regulatory frameworks that apply to the development and use of radiopharmaceuticals in the Netherlands, EU, and United States. Given the scope of this study, we elaborate more on the regulatory frameworks in the Netherlands than on the EU and the USA. As the Dutch regulatory framework is primarily derived from general EU regulations, we will provide more information on the EU regulatory framework than in the framework in the USA.

A.1 Regulatory frameworks in the Netherlands

This section aims to highlight any Dutch regulations with brief reference to EU legislation (see section A.2) where necessary. This section is divided into two: the first sub-section outlines the main legislative acts relevant for the regulation of pharmaceutical products, and the second sub-section outlines the main legislative acts related to safety and use of radioactive materials.

A.1.1 Pharmaceutical regulation

A.1.1.1 R&D and clinical research

The Dutch Medical Research Involving Human Subjects Act (*Wet medisch-wetenschappelijk onderzoek met mensen, WMO*) safeguards participants in clinical research. Other relevant decrees include:

- Medical research involving human subjects compulsory insurance decree *(Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen)*.
- Medical research involving human subjects regulation *(Regeling medisch-wetenschappelijk onderzoek met mensen)*.
- Individual healthcare professions act *(Wet op de beroepen in de individuele gezondheidszorg, BIG)*.

At European level, relevant legislation includes European Directive 2005/28/EC (Good Clinical Practice Directive) and European Regulation 536/2014 (Clinical Trials Regulation).

A.1.1.2 Market access

Marketing authorisation is regulated at European level by Regulation 726/2004 and assessed by the EMA. In the Netherlands, the Dutch Medicines Evaluation Board (*College ter Beoordeling van Geneesmiddelen (CBG)*) approves marketing authorisation for the Netherlands under the scope of the Dutch Medicines Act (*Geneesmiddelenwet, GnW*).

The Dutch Price of Drugs Act (*Wet Geneesmiddelprijzen, Wgp*) provides the legal basis for the setting of prices for medicines. The Dutch system relies on external reference pricing (ERP),

which calculates prices as an average of the price of (similar) medicines in Belgium, France, Norway, and the United Kingdom.[159]

The Dutch Healthcare Insurance Act (*Zorgverzekeringswet, Zvw*) sets out which pharmaceutical products or treatments are covered by the 'basispakket' – the obligatory healthcare insurance for all Dutch citizens. Products used in hospitals (also referred to as intramural, or in-patient, treatment), which includes radiopharmaceuticals, are often allowed into the 'basispakket' without any special price negotiations. For pharmaceutical products where prices are deemed too high, the product is locked in further assessment of its necessity, effectiveness, cost effectiveness and feasibility, which may be followed by price negations after which the product can be allowed into the 'basispakket'.[160] This lock is called the 'sluis voor dure geneesmiddelen'. Currently, the only radiopharmaceutical in this lock is Lutetium-177 vipivotide tetraxetan (Pluvicto®), a radiopharmaceutical used to treat progressive metastatic castration-resistant PSMA-positive prostate cancer.[161] Products not allowed in to the 'basispakket' because there is insufficient evidence of the effectiveness over existing treatments can access temporary financing through the *Subsidieregeling veelbelovende zorg*.[162]

The Dutch Healthcare (Market Regulation) Act *(Wet marktordening gezondheidszorg, Wmg)* outlines the funding of inpatient treatment with medicinal products in hospitals.

A.1.1.3 Production, manufacturing, and distribution

The Dutch Medicines Act (GnW) aligns with *Directive 2001/83/EG*, guiding the production and sale of medicinal products. The *Council Directive 93/42/EEC on Medical Devices* is integrated into the Dutch *Medical Devices Act (Wet medische hulpmiddelen).*

The European Union also sets out standards for good manufacturing practices. National inspections take place to ensure compliance. In The Netherlands, the Dutch Health and Youth Care Inspectorate *(Inspectie Gezondheidszorg en Jeugd, IGJ)* carries out inspections under the scope of the Dutch Medicines Act *(Geneesmiddelenwet, GnW).*

A.1.2 Safety in and use of radiopharmaceuticals

Regulations for the specific use and application of nuclear medicine, implemented by the Supply Agency of the European Atomic Energy Community (EURATOM), and general regulations on the clinical use and pharmaceutical application, implemented by the European Commission, are adapted to Dutch Ministerial Regulations that provide an outline for public and private use of nuclear medicine within the Netherlands.

159 Rijksoverheid.nl (n.d.). Betaalbaar houden van medicijnen. Rijksoverheid.nl.
Available at: https://www.rijksoverheid.nl/onderwerpen/geneesmiddelen/betaalbaar-houden-van-geneesmiddelen
160 Zorginstituutnederland.nl (n.d.). Sluis voor dure geneesmiddelen.
Available at: https://www.zorginstituutnederland.nl/over-ons/programmas-en-samenwerkingsverbanden/horizonscan-geneesmiddelen/sluis-voor-dure-geneesmiddelen
161 Zorginstituutnederland.nl (n.d.). Overzicht geneesmiddelen in de sluis.
Available at: https://www.zorginstituutnederland.nl/over-ons/programmas-en-samenwerkingsverbanden/horizonscan-geneesmiddelen/sluis-voor-dure-geneesmiddelen/overzicht-geneesmiddelen-in-de-sluis
162 Zorginstituutnederland.nl (n.d.). Veelbelovende zorg: subsidieregeling voor onderzoek naar potentieel veelbelovende zorg.
Available at: https://www.zorginstituutnederland.nl/werkagenda/veelbelovende-zorg

The Dutch Medicines Act (GnW) ensures safe medicine use through reporting side effects, online prescription rules, and potential fines for violation of safety practices in the production, storage, transport of medicinal products.

A set of nuclear regulations adapted by the Netherlands concern the protection and production standards of ionising radiation devices (see Table 9).

Dutch Regulation	Main aims
Laws: Wetten	
Nuclear Energy Law *(Kernenergiewet)*	The Act forms the legal foundation for decisions and regulations in radiation protection. It sets guidelines for nuclear energy release in radioactive and ionising radiation devices.
Population Survey Act *(Wet op het Bevolkingsonderzoek)*	The Act safeguards against risks in radioactive exposure regarding procedures such as medical screening, permits for clinical testing and conducting population analysis.
Individual Health Care Professions Act *(Wet op de beroepen in de individuele gezondheidszorg)* & Law on Special Medical Operations including the Radiation Protection Medical Exposure Scheme *(Wet op de bijzondere medische verrichtingen)*	These laws define rules for healthcare professions, although not specific to nuclear medicine, it includes healthcare professionals working within healthcare settings operating medical devices that utilise radiation, such as radiotherapy.
Quality Act on Healthcare Institutions *(Kwaliteitswet zorginstellingen)*	This law focuses on providing guidelines on quality that Dutch healthcare institutions should adhere by to maintain optimal safety and health standards.
The Environmental Protection Act *(Wet Milieubeheer), since January 2024 replaced by the Omgevingswet* & The General Administrative Act *(Algemene wet bestuursrecht)*	The General Administrative Act outlines which nuclear installations are subject to The Environmental Acts which defines the protocol for radioactive waste management.
Decrees: Algemene Maatregelen van Bestuur (AMvB's) en andere Koninklijke Besluiten	
Decision on training requirements and area of expertise radiodiagnostic laboratory technician and radiotherapeutic laboratory technician *(Besluit opleidingseisen en deskundigheidsgebied radiodiagnostisch laborant en radiotherapeutisch laborant)*	The Decision refers to the rules and guidelines on training personnel, such as radiodiagnostic and radiotherapeutic laboratory technicians.
Decision on training requirements and field of expertise clinical physicist *(Besluit opleidingseisen en deskundigheidsgebied klinisch fysicus)*	The Decision provides rules on the training and expertise of clinical physicists.

Dutch Regulation	Main aims
Regulation: Ministeriële Regelingen	
Basic Safety Standards Radiation Protection (Rbs Scheme) *(Regeling basisveiligheidsnormen stralingsbescherming (Rbs))*	The regulation includes guidance and elaboration on trainings and expertise on radiation protection.
Radiation Protection Occupational Exposure Scheme 2018 *(Regeling stralingsbescherming beroepsmatige blootstelling 2018)*	The regulation refers to the radiation protection of employees and further elaborate the guidelines in this scheme.
Radiation protection medical exposure scheme *(Regeling stralingsbescherming medische blootstelling)*	The regulation provides guidance and elaboration around the protection of radiation for patients that are exposed to medical-radiological equipment.
ANVS Regulation on basic safety standards radiation protection (Vbs) *(ANVS- verordening basisveiligheidsnormen stralingsbescherming (Vbs))*	The Authority for Nuclear Safety and Radiation Protection (ANVS) lays down additional technical and organisational guidelines and rules for the protection around radiation[163,164].

Table 9 **Nuclear Regulations in the Netherlands**

The ANVS is responsible for maintaining the highest safety and radiation protection standards across the nuclear industry in the Netherlands. The ANVS establishes guidelines for rules and issuing of licenses for the nuclear medicine industry and its related support services. The resources provided by ANVS include Guidelines on the Safe Design and Operation of Nuclear Reactors, nuclear safety and radiation protection measures, registration services for practitioners and experts, transport measures, stress tests for nuclear installations and the facilitation of applications for the extension of nuclear power plants. The ANVS is responsible for completing an Integrated Regulatory Review Service (IRRS) each year. A team of international experts assess the national system of nuclear safety and radiation protection[165].

As a consequence of nuclear medicine production, radioactive waste needs to be managed throughout the production process. The Central Organisation for Radioactive Waste (COVRA) manages the total quantities of spent fuel and radioactive waste generated in the production of nuclear medicine in the Netherlands[166].

A.2 Regulatory frameworks in the EU

The European Commission (EC) plays a central role in establishing legislation for nuclear medicine at EU level. It is involved in the harmonisation of legislation that ensures institutions, organisations and industries across the EU adhere to safety and standardisation regarding radioactive materials and radiopharmaceuticals.

163 European Nuclear Safety Regulators Group, ENSREG. (n.d.). Available at: https://www.ensreg.eu/country-profile/Netherlands
164 Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Nuclear Medicine, Overview of legislation. (2018). Available at: https://www.rivm.nl/medische-stralingstoepassingen/trends-en-stand-van-zaken/wetgeving-en-richtlijnen/overige-nederlandse-wetgeving#Nederlandse%20wet-%20en%20regelgeving
165 Authority for Nuclear Safety and Radiation Protection (ANVS). (n.d.). Available at: https://english.autoriteitnvs.nl
166 COVRA NV, Radioactive Waste. (2024). Available at: https://www.covra.nl/nl/

Pharmaceutical products, including radiopharmaceuticals, are regulated in the EU by the general pharmaceutical legislation. The current pharmaceutical legislation is made up of Directive 2001/83 and Regulation 726/2004, which cover the conditions for the manufacture and marketing of (radio)pharmaceuticals in the EU. In April 2023, the Commission presented a proposal for a new pharmaceutical legislation, including a new Directive[167] and Regulation[168]. Both newly proposed instruments will apply to radiopharmaceuticals. The focus of this revised legislation is on better access, the creation of a Single Market for medicines, promotion of innovation and competitiveness, and promotion of public health interests, among others. The proposals are not yet in force; at the moment, Member States can evaluate and comment on the proposed measures.

The European Union has many Regulations, Directives, Delegated Regulations, or Implementing Regulations which contribute to the pharmaceutical landscape in the EU. Key Regulations or Directives relevant to the regulation of radiopharmaceuticals include:

- **Commission Directive (EU) 2017/1572 of the European Parliament as regards the principles and guidelines of good manufacturing practice for medicinal products of human use**, focuses on the principles of good manufacturing practices (GMP) for general medicinal products and radiopharmaceuticals used in healthcare settings. It provides standard guidelines for manufacturing, quality control, and distribution of medicinal products, ensuring that the standards are adhered to. This Directive highlights overall the quality assurance that should be followed in nuclear medicine.
- **Regulation (EU) 536/2014 on Clinical Trials for medicinal products for human use (CTR) and Directive 2001/20/EC** set out the rules for conducting clinical trials with medicinal products in the EU. Ensuring guidelines for safety and efficacy of new medicines, including radiopharmaceuticals. It further establishes a standardised process for authorisation and supervision of clinical trials across the EU. The regulation is intended to make it easier to conduct multinational clinical trials across the EU.
- **Directive 2001/83/EC on Medicinal Products for Human Use** provides a regulatory framework for the use of medicinal products (human use) within the EU. The framework addresses marketing authorisation, quality, safety, and pharmacovigilance. It sets regulations for good clinical practices in the conduct of clinical trials.
- **Regulation (EC) No 726/2004** lays down the procedures for the authorisation and supervision of medicinal products and the role of the European Medicines Agency. It provides a regulatory framework for the role, functioning and procedures of the EMA.
- **Pharmacovigilance Regulation No 1235/2010, with amending (EU) No 1027/2012** establishes a monitoring framework that ensures the safety of medicinal products throughout their lifecycle. This includes managing transparent exchange and reporting of adverse drug reactions (ADRs) in patient safety.
- **Directive 2010/84/EU, with amending Directive 2012/26/EU** harmonises procedures for reporting, evaluation, and patient safety. This includes assessment of risk management plans, post-authorisation safety reporting and coordination and evaluation of pharmacovigilance inspection.

167 Proposal for a Directive on the Union code relating to medicinal products for human use.
168 Proposal for a Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency

- **Commission Delegated Regulation (EU)2017/1569**, provides technical specifications about the safety of dosage and monitoring exposure in radiopharmaceuticals. The Regulation aims to ensure a consistent and high level of safety standards across the EU.

Euratom is an international organisation that focuses on the safe use of nuclear energy within the EU. It establishes frameworks for organisations manufacturing and developing nuclear radioactive materials, particularly in the application of medicine.

The following regulations have been implemented by Euratom;

- **EURATOM Basic Safety Standards (BSS) Directive (2013/59/Euratom)** outlines fundamental principles and requirements for basic safety protection standards that individuals working within the radiopharmaceutical industry (exposed to radioactive materials) need to follow. This directive is for the guidance of individuals that work in medical and manufacturing settings.
- **Medical Exposure Directive (2013/59/Euratom)** addresses the specific requirements of protecting patients and physicians from exposure to radioactive materials. This includes dose limits and guides for the safe use and administration of medical procedures that include radiopharmaceuticals.
- **Radiation Protection Directive (2013/59/Euratom)** is a consolidated regulatory framework that modernises previous EU directives related to radiation protection. It covers various aspects such as occupational exposure, public exposure, emergency preparedness, waste disposal and the quality of radioactive materials.
- **Radiation Protection series publications** is a European Commission publication for topics on Energy. It has a series of publications and guidelines on the use of radiation since 1976.

Most of the regulation of Euratom and the EC concern directives that need to be implemented in national regulation of Member States. They set the minimum for these regulations for Member States, but national regulations may be implemented more strictly. This means that national regulation between EU Member States may be harmonised, but not identical. National differences exist and procedures and involved institutions differ.

Currently, under the SAMIRA action plan the EC has established a platform and launched actions to coordinate the implementation of Euratom's requirements for radiation protection in medicine with EU health regulation and policy. To that end, the Simplerad study (lead by the EANM) was launched to better understand the links and interrelations between the EU pharmaceutical legislation and the Euratom's requirements for radiation protection. This should lead to actions for a more coherent implementation of EU legal requirements for therapeutic nuclear medicine.

Table 10 Summary overview of EU regulatory frameworks

Key Actors	
Implementor	• European Commission • European Parliament • EURATOM
Regulations	• EURATOM Basic Safety Standards (BSS) Directive (2013/59/Euratom) • Medical Exposure Directive (2013/59/Euratom) • Radiation Protection Directive (2013/59/Euratom) • Radiation Protection series publications • Directive 2001/20/EC and Regulation 726/2004 • Commission Directive (EU) 2017/1572 of the European Parliament as regards the principles and guidelines of good manufacturing practice for medicinal products of human use • Commission Delegated Regulation (EU) 2017/1569 • Regulation (EU) 536/2014 on Clinical Trials for medicinal products for human use (CTR) and Directive 2001/20/EC • Directive 2001/83/EC on Medicinal Products for Human Use • Pharmacovigilance Regulation No 1235/2010, with amending (EU) No 1027/2012 • Directive 2010/84/EU, with amending Directive 2012/26/EU

A.3 Regulatory frameworks in the USA

The USA has a relatively simple regulatory framework for nuclear medicine compared to Europe. The two key organisations involved in the regulation of radiopharmaceuticals are the federal Food and Drug Administration, which regulates the approval, use and (clinical) research in nuclear medicine, and the federal Nuclear Regulatory Commission (NRC) who has regulatory oversight over the use of nuclear material in the US.

The Food and Drug Administration (FDA) is a federal agency that is responsible for safeguarding and regulating the approval, production, marketing, and use of medicinal products across the USA. The FDA evaluates the safety and effectiveness of radiopharmaceuticals through pharmacovigilance in ensuring the safety, efficacy, and quality of these products. The Federal Food, Drug, and Cosmetic Act provides a legal framework for enforcing safety standards in the manufacturing, marketing, and distribution of medicinal products[169].

The Nuclear Regulatory Commission (NRC) is an independent agency with the mandate to guarantee the secure use of radioactive materials for beneficial purposes whilst protecting users and the environment. The NRC's mission is to regulate commercial nuclear power plants and other uses of nuclear materials, including their use in nuclear medicine. This oversight involves the issuance of licenses, enforcing compliance with established requirements to

169 U.S Food and Drug Administration, Source: https://www.fda.gov

safeguard both people and the environment, as well as conduct inspections[170]. This is done by providing quality guidelines and hosting conferences to maintain a network between the chain of different players within the nuclear medicine sector. NRC, therefore, acts as facilitator between stakeholders within the nuclear medicine sector and hosts public meetings in which citizens are encouraged to participate and provide input. Federal facilities such as the Department of Defence hospitals and the Department of Veterans Affairs hospital are regulated by the NRC (rather than by the state in which the facility is located). Title 10, Code of Federal Regulations (1-199) addresses compliance measures with accordance to;

- **Licensing Requirements**: Indicating the procedure for obtaining the appropriate licensing to use radioactive materials in nuclear medicine.
- **Radiation Safety Standards**: Addressing the necessary precautionary standards required to safely use radioactive materials to protect workers and the environment during the production and use of radiopharmaceuticals and radioisotopes.
- **Security measures**: Defining standards of security to prevent the theft or sabotage of radioactive materials.
- **Quality Assurance and Control**: Establishing criteria for quality assurance and control processes to ensure the safe use of radiopharmaceuticals in manufacturing and handling standards.
- **Inspections and Enforcement**: Describing the features for regulatory inspections, reporting requirements and compliance standards. This includes observing penalties for non-compliance.
- **Training and Qualifications**: Setting standards for training and qualifications of personnel involved in the production, handling, and administration of radioactive materials in nuclear medicine.
- **Waste management**: Providing guidelines for the correct disposal and management of radioactive waste generated during the production and use of radiopharmaceuticals.

The NRC established a committee for the regulation of medical uses of radioactive material (ACMUI). The committee advises the NRC on technical and policy concerns that may arise in diagnosis or therapy[171]. The operational practices of the ACMUI are monitored and governed by the Federal Advisory Committee Act (FACA).

Due to the sensitive nature of radioactive materials, ensuring the safety of transportation is crucial. The U.S. Department of Transportation regulates the movement of nuclear radiopharmaceuticals according to the regulation on Hazardous Materials and Oil transportation[172]. The movement of goods is therefore overseen at national level. Furthermore, the Pipeline and Hazardous Materials Safety Administration (PHMSA) assists in mapping out the dynamic and challenging ecosystem of hazardous materials, including radiopharmaceuticals, to ensure continuous innovation and safe transportation of these materials[173].

170 U.S. Nuclear Regulatory Commission, Source: https://www.nrc.gov/materials/miau/med-use.html and https://www.nrc.gov/about-nrc/radiation/protects-you/reg-matls.html
171 Advisory Committee on the Medical use of Isotopes, U.S. Nuclear Regulatory Commission, Source: https://www.nrc.gov/about-nrc/regulatory/advisory/acmui.html
172 Code of Federal Regulations, Source: https://www.ecfr.gov/current/title-49/subtitle-B/chapter-I
173 Pipeline and Hazardous Materials Safety Administration, Source: https://www7.phmsa.dot.gov/about-phmsa/phmsas-mission

Key Actors	
Implementors	• Food and Drug Administration • Nuclear Regulatory Commission (NRC) • ACMUI • Pipeline and Hazardous Materials Safety Administration (PHMSA)
Regulation	• The Federal Food, Drug, and Cosmetic Act • Title 10, Code of Federal Regulations, sections 201 of the Energy Reorganisation Act of 1974, as amended 56 FR 29407, June 27, 1991[174] • Federal Advisory Committee Act (1972)[175] • Pipeline Safety Regulations (Title 49 CFR Parts 190-190)[176]

174 Title 10, Code of Federal Regulations, section 201 of the Energy Reorganisation Act of 1974, as amended 56 FR 29407, June 27, 1991, Nuclear Regulatory Commission. Source: https://www.nrc.gov/reading-rm/doc-collections/cfr/index.html

175 U.S. General Services Administration, Source: https://www.gsa.gov/policy-regulations/policy/federal-advisory-committee-management/legislation-and-regulations/federal-advisory-committee-act?_gl=1*1iy2u72*_ga*MjAyMTcwNjY0NC4xNzAxMzM2Mjkw*_ga_HBYXWFP794*MTcwMTMzNjI5MC4xLjEuMTcwMTMzNjMwMi4wLjAuMA

176 Code of Federal Regulations, Source: https://www.ecfr.gov/current/title-49

Appendix B
List of identified actors in the Dutch innovation ecosystem for nuclear medicine

Type	Type detail	Organisation	City
Afdeling nucleaire geneeskunde	Academisch ziekenhuis - Afdeling nucleaire geneeskunde	Amsterdam UMC	Amsterdam
Afdeling nucleaire geneeskunde	Academisch ziekenhuis - Afdeling nucleaire geneeskunde	Erasmus MC	Rotterdam
Afdeling nucleaire geneeskunde	Academisch ziekenhuis - Afdeling nucleaire geneeskunde	LUMC	Leiden
Afdeling nucleaire geneeskunde	Academisch ziekenhuis - Afdeling nucleaire geneeskunde	Maastricht UMC	Maastricht
Afdeling nucleaire geneeskunde	Academisch ziekenhuis - Afdeling nucleaire geneeskunde	Radboudumc	Nijmegen
Afdeling nucleaire geneeskunde	Academisch ziekenhuis - Afdeling nucleaire geneeskunde	UMC Groningen	Groningen
Afdeling nucleaire geneeskunde	Academisch ziekenhuis - Afdeling nucleaire geneeskunde	UMC Utrecht	Utrecht
Beroepsvereniging	Beroepsvereniging - Klinische fysica	NVKF	Utrecht
Beroepsvereniging	Beroepsvereniging - Multidiciplinair	PSMAForum	Dordrecht
Beroepsvereniging	Beroepsvereniging - Nucleaire geneeskunde	NVNG	Breda
Beroepsvereniging	Beroepsvereniging - Radiochemie	NKRV	Nederland
Beroepsvereniging	Beroepsvereniging - Ziekenhuisapothekers	NVZA	Utrecht
Farmaceut	Farmaceut - Gevestigd	Curium Pharma	Petten
Farmaceut	Farmaceut - Gevestigd	Novartis/AAA	Baarle-Nassau
Farmaceut	Farmaceut - Gevestigd	Novartis	Amsterdam
Farmaceut	Farmaceut - Gevestigd	Quirem Medical/ Terumo Europe	Deventer
Farmaceut	Farmaceut - Gevestigd	GE Healthcare	Leiderdorp

Type	Type detail	Organisation	City
Farmaceut	Farmaceut - Gevestigd	GE Healthcare	Zwolle
Farmaceut	Farmaceut - Startup	TerThera	Breda
Producent	Producent - Startup	AlfaRim	Delft
Industrievertegen-woordiging	Industrievertegenwoordiging - Farma	VIG	Den Haag
Industrievertegen-woordiging	Industrievertegenwoordiging - Farma/equipment	NMEU	Brussel
Industrievertegen-woordiging	Industrievertegenwoordiging - Nucleaire sector	Nucleair Nederland	Nederland
Leverancier	Leverancier - Equipment	Comercer NL	Joure
Leverancier	Leverancier - Equipment	Van Overeem Nuclear	Breda
Leverancier	Leverancier - Equipment	Zereau	Nijmegen
Leverancier	Leverancier - Equipment	Elekta/Nucletron	Veenendaal
Leverancier	Leverancier - Equipment	Von Gahlen	Zevenaar
Leverancier	Leverancier - Equipment	MILabs	Utrecht
Leverancier	Leverancier - Equipment	PI Medical	Raamsdonkveer
Leverancier	Leverancier - Equipment	FOR-MED / Vanderwilt Techniques	Boxtel
Leverancier	Leverancier - Equipment	MetorX	Goedereede
Leverancier	Leverancier - Equipment	2Quart Medical	Schagen
Leverancier	Leverancier - Equipment	MNT Kwint International	Waardenburg
Leverancier	Leverancier - Equipment	Siemens Healthineers	Den Haag
Leverancier	Leverancier - Equipment	GE Healthcare Systems	Hoevelaken
Leverancier	Leverancier - Grondstoffen/Verrijking	URENCO	Almelo
Leverancier	Leverancier - Services	FutureChemistry	Wageningen
Overheid	Overheid - Ministerie	VWS	Den Haag
Overheid	Overheid - Toezichthouder/adviseur	RIVM	Bilthoven
Overheid	Overheid - Toezichthouder/adviseur	ANVS	Den Haag
Overheid	Overheid - Toezichthouder/adviseur	IGJ	Utrecht

Type	Type detail	Organisation	City
Overheid	Overheid - Toezichthouder/adviseur	EMA	Amsterdam
Overheid	Overheid - Toezichthouder/adviseur	ZIN	Diemen
Overheid	Overheid - Toezichthouder/adviseur	CBG	Utrecht
Patiëntenorganisatie	Patiëntenorganisatie	NFK	Utrecht
Patiëntenorganisatie	Patiëntenorganisatie	Prostaatkankerstichting	Utrecht
Producent	Producent - Medische isotopen met cyclotron	BV Cyclotron VU	Amsterdam
Producent	Producent - Medische isotopen met cyclotron	Cyclotron Noordwest BV	Alkmaar
Producent	Producent - Medische isotopen met cyclotron	Radboud Translational Medicine	Nijmegen
Producent	Producent - Medische isotopen met cyclotron	AccTec BV / GE Healthcare	Eindhoven
Producent	Producent - Medische isotopen met cyclotron	Cyclotron UMCG	Groningen
Producent	Producent - Medische isotopen met cyclotron	Cyclotron Rotterdam BV	Rotterdam
Producent	Producent - Medische isotopen met reactor	NRG	Petten
Producent	Producent - Medische isotopen met reactor	PALLAS	Petten
Producent	Producent - Medische isotopen met reactor	SHINE	Veendam
R&D	R&D - Clinical Trials	Tracer	Groningen
R&D	R&D - Clinical Trials	ICON	Groningen, Utrecht, Assen, Amsterdam
R&D	R&D - Faciliteiten & Samenwerking	FIELD-LAB	Petten
R&D	R&D - Onderzoek en onderwijs	TU Delft	Delft
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Admiraal de Ruyter Ziekenhuis	Goes
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Albert Schweitzer Ziekenhuis	Dordrecht
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Albert Schweitzer Ziekenhuis	Hendrik-Ido-Ambacht

Type	Type detail	Organisation	City
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Alexander Monro Ziekenhuis	Bilthoven
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Alrijne Ziekenhuis	Leiderdorp
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Amphia Ziekenhuis	Breda
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Bravis Ziekenhuis	Roosendaal
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Canisius-Wilhelmina Ziekenhuis	Nijmegen
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Catharina Ziekenhuis	Eindhoven
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Deventer Ziekenhuis	Deventer
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Diakonessenhuis	Utrecht
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Dijklander Ziekenhuis	Hoorn
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Elkerliek Ziekenhuis	Helmond
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Franciscus Gasthuis & Vlietland	Schiedam
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Gelre Ziekenhuizen	Apeldoorn
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Groene Hart Ziekenhuis	Gouda
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Hagaziekenhuis	Den Haag
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	HMC	Den Haag
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	HMC	Leidschendam
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	IJsselland Ziekenhuis	Capelle a/d Ijssel
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Ikazia Ziekenhuis	Rotterdam
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Isala	Zwolle

Type	Type detail	Organisation	City
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Isala	Meppel
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Jeroen Bosch Ziekenhuis	Den Bosch
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Laurentius Ziekenhuis	Roermond
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Maasstad Ziekenhuis	Rotterdam
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Martini Ziekenhuis	Groningen
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Maxima Medisch Centrum	Veldhoven
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	MC Leeuwarden	Leeuwarden
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Meander Medisch Centrum	Amersfoort
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Medical Specialist Center Vaals B.V.	Vaals
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Medisch Spectrum Twente	Enschede
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	NKI/Antoni van Leeuwenhoekziekenhuis	Amsterdam
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Noordwest Ziekenhuisgroep	Alkmaar
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	OLVG	Amsterdam
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Ommelander Ziekenhuis Groep	Scheemda
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Reinier de Graaf Gasthuis	Delft
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Rijnstate	Arnhem
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Saxenburgh Medisch Centrum	Hardenberg
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Slingeland Ziekenhuis	Doetinchem
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Spaarne Ziekenhuis	Haarlem

Type	Type detail	Organisation	City
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Spaarne Ziekenhuis	Hoofddorp
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	St. Anna Ziekenhuis	Eindhoven
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	St. Antonius Ziekenhuis	Utrecht
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	St. Antonius Ziekenhuis	Nieuwegein
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Streekziekenhuis Koningin Beatrix	Winterswijk
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Tergooi MC	Hilversum
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Treant Zorggroep	Emmen
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Treant Zorggroep	Hogeveen
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Instituut Verbeeten	Tilburg
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	VieCuri Medisch Centrum	Venlo
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Wilhelmina ziekenhuis Assen	Assen
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Zaans Medisch Centrum	Zaandam
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Ziekenhuis Amstelland	Amstelveen
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Ziekenhuis Gelderse Vallei	Ede
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Ziekenhuis Rivierenland	Tiel
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Ziekenhuisgroep Twente	Almelo
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Ziekenhuisgroep Twente	Hengelo (OV)
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Zuyderland Medisch Centrum	Heerlen
Afdeling nucleaire geneeskunde	Ziekenhuis - Afdeling nucleaire geneeskunde	Zuyderland Medisch Centrum	Sittard

Appendix C
Methodological overview

C.1 Research questions

#	Research question	Link to report section
1	What does the process from ideation to the use of radiopharmaceuticals look like?	2 & 2.1
1A	Which organisations are involved in this process in the Netherlands, the EU, and the US?	2.1 & 3.1
1B	What regulatory frameworks are in place for this process in the EU and US?	Appendix A
1C	What bottlenecks occur in this process in the Netherlands?	2.2
1D	How can these bottlenecks in the Netherlands be resolved?	5.2
2	What does the Dutch (innovation) ecosystem for nuclear medicine look like?	3 & 3.2
2A	Which players are active in this Dutch (innovation) ecosystem?	3.1
2B	What are the strengths and weaknesses of this Dutch (innovation) ecosystem for innovativeness and earning capacity?	3.3
2C	What are the opportunities and threats for this Dutch (innovation) ecosystem for innovativeness and earning capacity?	3.4
3	What is the position of the Dutch (innovation) ecosystem in the European playing field for the development of radiopharmaceuticals?	4 & 4.1.1
4	How can the innovativeness of the Dutch (innovation) ecosystem for nuclear medicine be increased?	5.2
5	How can the earning capacity of the Dutch (innovation) ecosystem for nuclear medicine be strengthened?	5.2

C.2 Methodological approach

For this study we made use of a variety of methods to collect data from literature and actors within the innovation ecosystem for nuclear medicine in the Netherlands and abroad. The used approach is visualised and further detailed in Figure 15. Based on the analysis of the collected data, this report was drafted and reviewed by the study's advisory group.

Desk and data studies	Round table discussions	In-depth interviews	Mini survey	Focus group	Analysis and synthesis	Validation workshop
Studies and research paper Policy and regulatory documents Books, articles, and magazines Websites, data-sources and position papers	Organised by the min. VWS which two of our researchers joined 3 sessions, which focused on fundamental research, transnational research, and clinical practice	17 one-hour interviews Semi-structured Questions were adapted based on expertise of the interviewee	32 respondents Questions on their perception on the Dutch ecosystem for nuclear medicine	9 companies present 2 hours, on location Discussion about their reflections on the survey results, their view on earning capacity and recommendations	Coded the notes from the round table discussions, interviews, and focus group in Atlas.ti Analysedand visualised the survey results in Excel Internal session with the team to discuss findings, form recommendations, and to align reporting	10 stakeholders were present for this online session of 1,5 hour The findings and conclusions from our analysis and synthesis were validated, and first recommendations were tested and refined

Figure 15 Methodological overview

The study's advisory group consisted of representatives from FAST (Marlous Kooijman and Paul Smits), the Ministry of VWS (Astrid Freytag), NVNG (Andor Glaudemans) and Oncode Institute (Alexander Turkin). Some of these representatives are also involved in DECISIVE.

An overview of consulted stakeholders in the in-depth interviews, focus group and validation workshop is provided in section C.3. For the survey 60 contact persons from across the identified actors in the innovation ecosystem for nuclear medicine were invited to participate. In total 32 (53%) invited contacts responded to the survey, of which 25 (43%) fully completed the survey, which is considered a fairly high response rate. No full responses were received from equipment suppliers nor from R&D organisations. Invitees received an invitation and up to two reminders when they had not completely filled out the survey. The survey's response statistics are provided in Table 11.

Type of respondent	Identified actors	Invited contacts[177]	Full responses	Full response rate
Departments of Nuclear Medicine in Hospitals	67	16	10	63%
Equipment suppliers	15	3	0	0%
Isotope producers	9	7	3	43%
Pharmaceutical companies	8	8	2	25%
Government organisations	7	14	6	43%
Professional associations	5	2	1	50%
Industry representation	3	2	2	100%
Patient organisations	3	4	1	25%
R&D in/for nuclear medicine (research (support) organisations apart from academic hospitals)	3	4	0	0%
Total	**120**	**60**	**25**	**42%**

Table 11 **Survey response statistics**

The conclusions in this report were drafted based on a synthesis of the key findings in this report. The conclusions address the key research questions. Recommendations were drafted based on the conclusion (section 5.1), SWOT (sections 3.3 and 3.4), identified barriers (section 2.2) and lessons from abroad (section 4.3) identified in the report. The relation between these is given in Table 12.

177 For some identified actors multiple contacts were invited in the survey.

#	Recommendation	Link with conclusion	Link with SWOT/barriers	Lessons from abroad
Recommendations to improve innovativeness				
1	Create a platform	• More collaboration and coordination are required to unlock full potential of ecosystem	• W: lack of collaboration and joint actions • B: fragmented R&D	• Organisation at EU level • Organisation and collaboration in Australia
2	Build a network of innovation centres	• More collaboration and coordination are required to unlock full potential of ecosystem • Most challenges experienced at clinical trials	• W: limited available funding (while high infrastructure costs) • W: limited collaboration • W: difficult to upscale to other centres • T: limited capacity of hospital infrastructure • B: lack of key infrastructure/insufficient hospital infrastructure	• Collaboration and network of hospitals in Australia
3	Create a roadmap for investigator-led R&D	• More collaboration and coordination are required to unlock full potential of ecosystem • Most challenges experienced at clinical trials	• W: fragmented R&D • O: anticipated advancements in nuclear medicine research	• Action at EU level with the SAMIRA Action Plan
4	Commit public-private funding to roadmap	• Available funding is considered a weakness	• W/B: limited available funding • T: losing forefront position	• Government funding in Australia for investigator-led early phase clinical research
5	Use platform for dialogue about regulation	• Market access is considered a barrier in the Netherlands	• W: stricture regulation and long procedures	• More favourable regulation in USA, Australia and in some respects Germany and other EU MSs

#	Recommendation	Link with conclusion	Link with SWOT/barriers	Lessons from abroad
Recommendations to improve earning capacity				
1	Organise dedicated valorisation support at innovation centres	Process from idea to use of a nuclear medicine can be improved Valorisation or research and translation into further phases of CTs is low Most challenges are experienced during CTs	W: commercialisation of nuclear medicine	-
2	Better market Dutch ecosystem for nuclear medicine	The Netherlands has internationally a strong reputation in nuclear medicine	T: growing shortage of qualified staff B: Dutch relatively small market W: limited available funding	-
3	Adress HC needs and requirements with education providers	Human capital and education (for radiation protection and nuclear medicine physicians) is considered a weakness	T/B: growing shortage of qualified staff O: anticipated advancements in nuclear medicine	Shortage of nuclear medicine physicians in the USA and changes in education in the USA
4	Strengthen demand side for nuclear medicine	-	T: limited capacity of hospital infrastructure O: anticipated advancements in nuclear medicine	Investments in infrastructure in Australia has given field a boost

Table 12 Link between recommendations, conclusions, SWOT, and lessons from abroad

C.3 Consulted stakeholders and experts

The researchers thank the following stakeholders and experts for their contribution to this study. They are displayed in alphabetical order.

Name	Organisation	Involvement
Alex Poot	UMC	Interview
Alexander Turkin	Oncode Institute/DECISIVE	Study advisory group
Andor Glaudemans	NVNG/DECISIVE	Interview & study advisory group
Astrid Freytag	Min. VWS	Study advisory group
Charlotte Rosenbaum	RIVM	Validation workshop
David Bailey	SHINE	Interview
Erik de Blois	ErasmusMC/DECISIVE	Interview
Erik Verburg	ErasmusMC/DECISIVE	Validation workshop
Every Romeyn	Novartis	Focus group
Fred Verzijlbergen	PSMAForum	Interview
Hanno Mak	AlfaRim	Focus group
Jan Guse	Novartis	Interview
Jan Sigger	Quirem Medical	Interview
Jeroen van Moorselaar	Amsterdam UMC	Validation workshop
Johannes Czernin	UCLA	Interview
Karlijn van Schilden	NRG/FIELD-LAB	Interview & validation workshop
Lars Perk	RTM	Interview & focus group
Lars Roobol	RIVM	Validation workshop
Ly Tran	BFAS (min. VWS)	Interview
Maarten Brom	TRACER	Interview
Marieke van Dok	Min. VWS	Interview
Mart-Jan Blauwhoff	NMEU	Validation workshop
Mattijs Maris	Zereau	Focus group
Nicole van de Water	Novartis	Interview
Onno Kaandorp	IGJ	Validation workshop
Paul Smits	FAST	Study advisory group
Peter Bertens	VIG	Focus group

Name	Organisation	Involvement
Peter Laverman	Radboudumc	Interview
Rene van der Steeg	SHINE	Focus group
Rick Henderik	Novartis	Interview
Robin Gommers	Novartis/AAA/IDB Holland	Focus group
Rudi Dierckx	EANM	Interview
Tamar Endeman	Min. VWS	Validation workshop
Tessa Aminetzah	TRACER	Interview
Vinod Ramnandanlal	NRG/FIELD-LAB	Interview & focus group
Walter Kool	NWZ	Focus group
Wim Oyen	Rijnstate en Humanitas University, kwartiermaker voor VWS	Interview & validation workshop
Winette van der Graaf	NKI	Validation workshop

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