EU Policy Symposium 1

Bridging the Gap: EU Pharma Legislation & Basic Safety Standards - Navigating Legal Complexity across Europe

At the EANM Annual Congress in Hamburg on October 22nd, 2024, the EANM **Policy & Regulatory Affairs Council** (PRAC) organised a policy symposium on radiopharmaceuticals´ regulatory considerations.
Given their unique nature, radiopharmaceuticals require a regulatory framework that addresses their specific characteristics and challenges. However, current European regulations are considering radiopharmaceuticals under the same umbrella as other medicinal products, constraining their development and delivery.

In the context of the revision of the EU Pharmaceutical Legislation and in view of the conclusion of the SIMPLERAD project, the co-chairs, Wim Oyen and Oliver Kiss, designed the symposium to address these issues, looking at good practices and potential solutions across Europe.

Words from the Co-Chairs

"We are deeply grateful for the insightful discussions and contributions at this symposium, which highlighted the pressing need for a harmonised and fit-for-purpose regulatory framework for radiopharmaceuticals across Europe.
As co-chairs, we emphasize the importance of leveraging the revision of EU Pharmaceutical Legislation and the findings of the SIMPLERAD project to address current regulatory complexities, foster innovation, and ensure equitable patient access to these critical medicinal products.
Together, we can build a more coherent and supportive environment for the development and delivery of radiopharmaceuticals, ultimately improving care for patients across Europe."

Wim Oyen & Oliver Kiss

Setting the scene

Georgi Simeonov, Directorate-General for Energy, European Commission

Georgi Simeonov provided a **comprehensive overview of the Euratom legal framework governing radiation protection in medicine** within the EU, based on the Basic Safety Standards (BSSD) Directive 2013/59/Euratom, including some of its key articles.

Georgi Simeonov then presented the **SAMIRA Action Plan**, an initiative under Europe's Beating Cancer Plan and the EU's first comprehensive plan to support the safe, high quality and reliable use of radiological and nuclear technology in healthcare. It is overseen by the Steering Group on Quality and Safety (SGQS) and engages health and radiation protection authorities across the EU and Norway. The plan is structured around three core workstreams:

1. **Ensuring medical radioisotope supply security** through the European Radioisotope Valley Initiative.
2. **Advancing quality and safety in medical ionising radiation** applications through the European Initiative on Quality and Safety of Medical Applications.
3. **Fostering innovation and technology development** by establishing a research roadmap for medical applications involving ionising radiation.

🔍 Key BSSD articles

- **Art. 4**: Defines "medical exposure" and "medical radiological" terms, standardising radiation protection across medical fields in the EU.
- **Art. 56**: Establishes optimisation in nuclear medicine, ensuring tailored, safe radiation doses for effective treatment.
- **Art. 83**: Details Medical Physics Experts' (MPE) roles in dosimetry and radiation protection, with involvement scaling by procedure complexity.
- **Art. 58**: Requires MPE roles to adapt to procedure needs, from limited in standard cases to extensive in high-risk treatments.
- **Art. 65**: Mandates public protection limits on radioactive discharge post-treatment, safeguarding carers and the public.

Simeonov highlighted the various SAMIRA/BSSD work programme related projects and tenders that have been developed in the past years, including CLAUD-IT, MARLIN, EU-REST and SIMPLERAD. He concluded with the newly established PrISMA Joint Action on "Preparatory activities to support Implementation of quality and Safety of Medical ionizing radiation Applications": the action offering direct support to Member States will be crucial in the next years to advance the medical applications in collaboration with all relevant stakeholders.

SIMPLERAD - SAMIRA Study on the implementation of the Euratom and the EU legal bases with respect to the therapeutic uses of radiopharmaceuticals*

Bernd J. Krause, Department of Nuclear Medicine. University Hospital Rostock

Professor Bernd J.Krause outlined the **SIMPLERAD project.** Its main **goal was to harmonise the requirements of the EU pharmaceutical legislation with the Euratom radiation protection requirements** (Directive 2013/59/Euratom) with respect to therapeutic use of radiopharmaceuticals.
To address the regulatory gaps identified over the course of the project, the consortium proposed practical guidance and recommendations to advance a coherent implementation of these requirements.

SIMPLERAD identified ten challenges in the regulation, implementation, and operational aspects of radiopharmaceuticals in Europe.

- **Regulatory and guidance gaps**: the consortium highlighted a lack of European guidance for implementing the Basic Safety Standards Directive (BSSD), as well as gaps in EMA guidance on radionuclide safety, resulting in unclear requirements for optimisation, dosimetry, and dose constraints in nuclear medicine.
- **Knowledge and expertise challenges:** Many nuclear medicine centres face a shortage of medical physics expertise and limited physician knowledge of dosimetry, compounded by divergent interpretations of standardised therapeutic procedures across the EU.
- **Operational and implementation issues**: Challenges identified included insufficient data for dosimetric treatment verification, inconsistent criteria for patient release and radioactive waste management, and unclear optimisation requirements under European directives.

The ambiguities with regards to the interdependencies between the EU pharmaceutical legislations and the BSSD, as well as the v**ariations in interpreting and implementing the BSSD across Member States** pose key challenges.

Krause emphasised that the final report would consolidate findings, and these recommendations will soon be published, so stay tuned for further details.

🔍 Highlighted SIMPLERAD Recommendations

- **Clarify Regulatory Precedence**: EMA and DG ENER should clarify the BSSD's precedence over pharmaceutical regulations for radiopharmaceuticals, with specific guidance on diagnostic and therapeutic applications.
- **Establish a Radiopharmaceuticals Expert Group**: EMA should create a permanent expert group with specialists in medical physics, radiopharmacy, and clinical nuclear medicine to oversee radiation safety and dosimetry standards.
- **Form a Multi-Level Regulatory Forum**: A coordinated forum among EMA, DG ENER, and national regulators is needed to align radiation safety and pharmaceutical regulations across the EU.
- **Develop Centres of Excellence** across Europe, supported by targeted training, to address Nuclear Medicine staffing shortages and standardise dosimetry practices.

** This text provides an informal summary of the session and is not officially authorised by the presenter.*

The National Outlook: Cases from two European countries – Netherlands and Switzerland

Switzerland: a role model for the Pharma & Radiation Protection interrelations?

Rolf Hesselmann, Scientific Federal Office of Public Health, Switzerland

Dr. Rolf Hesselmann presented Switzerland as a potential model for integrating pharmaceutical and radiation protection frameworks. Switzerland **follows European standards** (GMP, BSS, Ph.Eur.) **while maintaining national processes** for marketing authoriations and clinical trials.

Regulatory Structure

Swissmedic and the Radiation Protection Division of the Federal Office of Public Health (FOPH) **collaborate to regulate radiopharmaceuticals and are supported by a permanent commission of external experts** and by the Institute of Radiation Physics for product testing Foreign medications can be imported if no equivalent Swiss product exists, with NM physicians responsible for their usage.

Early Access and Clinical Trials

Swiss regulations provide three early access pathways through temporary authorisations: allowing patient access to treatments nearing Phase III completion, those unavailable domestically, or based on foreign trials with physician-led risk assessments. The Formula Magistralis exemption permits in-house preparations for specific patients.

Regarding clinical trials, they fall into three categories, each requiring different levels of oversight based on product authorisation and trial nature:

Category	Description	Approval Requirements
Category A	Trials using authorised products in compliant ways	Approval only from the Ethics Committee
Category B	Trials using authorised products in non-compliant ways	Ethics Committee and Swissmedic oversight required
Category C	Trials involving unauthorised products	Evaluation from the Ethics Committee, Swissmedic, and FOPH required; FOPH specifically assesses radiopharmaceutical quality

Dr. Hesselmann highlighted Switzerland's **integrated regulatory approach**, involving external experts and direct interaction of internal experts to ensure safe, efficient radiopharmaceutical processes as its key positive elements.

Navigating Legal Complexity across Europe: a Dutch case study

Marieke van Dok, Programme Director Medical Isotopes at the Ministry of Health, Welfare and Sport, Netherlands

Marieke van Dok shared how the Netherlands translates EU legislation into Dutch healthcare policy.
The Ministry of Health broadly aims at maintaining the "triple A" framework: availability, accessibility and affordability in healthcare.

🔍 Netherlands: Key Priorities

- **Technology-Neutral Legislation**: Essential for adaptability to new innovations.
- **Harmonized EU Regulations**: Misaligned rules across Member States could impede nuclear medicine advancements.
- **Support for Large Multicenter Trials**: Vital for cross-border nuclear medicine initiatives.
- **Interdisciplinary Collaboration**: Engage regulatory bodies, regulators, stakeholders, and end-users early in updates.

Regulatory Landscape

The Netherlands benefits from a comparatively flexible regulatory framework in nuclear medicine, as well as the execution and application of it by the regulators, with only a few regulators distributed across different regions. This broad interpretation of regulations allows for **more freedom in clinical research settings**, using exemptions and exceptions for clinical applications where contamination risks may demand larger production batches.
The regulatory structure under GMP-Z (Good Manufacturing Practice for non-commercial settings) allows hospital pharmacies flexibility, supporting academic expertise and local production of medications, where products are approved by in-house pharmacists rather than centralised authorities. This flexibility preserves academic knowledge and expertise crucial for advancing nuclear medicine.

Trends in Nuclear Medicine

The Dutch nuclear medicine field has shifted from being previously constrained by few registered options and minimal in-house pharmaceutical preparation, the field now has enabled broader treatment options and drug development. Future expectations include a rise in patient numbers and advancements in personalised dosimetry, with the introduction of more isotopes, such as alpha emitters, to offer tailored therapeutic solutions.

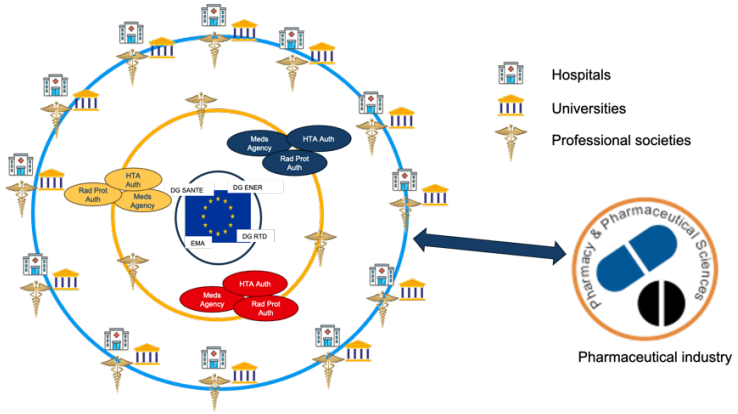
Solving the issue?

Anna Sundlöv, Clinical Assessor, Swedish Medical Products Agency

Dr. Anna Sundlöv, started with showcasing the reasons behind the legal complexities across Europe. She indeed highlighted **regulatory compartmentalization challenges** in the EU's nuclear medicine and radiopharmaceutical sectors. She noted **limited collaboration between regulators**, stemming from a lack of interaction, ownership, and shared terminology. The absence of established forms of interactions between radiation protection authorities, medicine agencies and HTA authorities limits regulatory effectiveness across Member States.

To address these issues, the **PrISMA Joint Action** was launched in 2024 under the EU4Health programme as a direct grant to Member State authorities. Concluding in late 2025, its final report will outline the groundwork for the future **SAMIRA Joint Action**. A key focus is radionuclide therapy, addressing regulatory actions recommended by the SIMPLERAD project through cooperation between European and national bodies and professional stakeholders.

To enhance communication and alignment, the Joint Action proposes a "concentric circle" framework to strengthen collaboration among regulators and stakeholders in therapeutic nuclear medicine:



- **Inner Circle (EU-level regulatory bodies)**: EU bodies establishing harmonised legislation to align standards across Member States, and considering specific grants and programmes for research and training.
- **Middle Circle (National regulatory bodies)**: National regulators ensuring consistent practices through joint training in radionuclide therapy and dosimetry and coordinating with HTA and audit authorities to standardise dosimetry, waste management and patient release criteria.
- **Outer Circle (Universities, hospitals, and professional societies)**: Stakeholders at the origin of a network of Centres of Excellence for education, clinical trials, dosimetry registries.

Sundlöv concluded with a **call for structured, multi-layered cooperation to streamline nuclear medicine regulations and reduce compartmentalization** across the EU.

Key Policy Recommendations

1. Calling all stakeholders to collaborate to raise awareness of Nuclear Medicine specificities across regulators, and the understanding of the Euratom frameworks & pharmaceutical requirements among the Nuclear Medicine Community. A key element includes the increase of relevant specialist knowledge with national competent authorities.

2. Calling EU institutions to **promote structured, yet flexible multi-tiered cooperation at all levels.** This should include increased collaboration between national regulators, across Member States and between EU regulators. This is crucial to make progress towards harmonisation of EU laws across all Member States. **This could take the form a Multi-Level Regulatory Forum**, as a coordinated forum among EMA, DG ENER, and national regulators to align radiation safety and pharmaceutical regulations across the EU.

3. Calling EU institutions and Member States to consider the unique specificities of radiopharmaceuticals when finalisng the revision of the EU Pharmaceutical Legislation.

4. Calling national regulatory authorities collaborating in the framework of the Joint Action PrISMA to ensure **that all relevant stakeholders are included in discussions about the future of RLT,** and to **leverage the existing frameworks and good practices.** Notable examples include Switzerland's integrated regulatory model and the Netherlands' flexible framework.

5. Calling universities, hospitals, and professional societies to collaborate in **establishing Centres of Excellence** dedicated to nuclear medicine cancer treatments. These centres would serve as hubs for research, innovation, and training, fostering the development of cutting-edge techniques and practices. Such centres will contribute to address Nuclear Medicine staffing shortages and standardise dosimetry practices.

6. Calling professional societies to collaborate with clinical centers in **establishing clinical data registries and databases on clinical factors for already approved radiopharmaceuticals focusing on dosimetry and outcomes**. Such a registry would provide a valuable resource for monitoring the safety and effectiveness of nuclear medicine procedures, facilitating evidence-based improvements.