Nuclear medicine therapy

REGULATORY DEVELOPMENTS

Carlo Chiesa

Ideas, materials, & slides provided by

Katarina Sjogreen-Gleisner, Glenn Flux, Manuel Bardies: EFOMP SIGFRID

Elena Solfaroli Camillocci, Istituto Superiore Sanità, Rome

DISCLOSURE SLIDE

In the last 3 years I was paid as speaker at meetings by

- Boston Scientific, producer of ^{90}Y glass microspheres
- Terumo, distributor of ^{166}Ho microspheres
- AAA-Novartis, producer of ^{177}Lu DOTATATE

I received a research grant from

- Boston Scientific, producer of ^{90}Y glass microspheres

European Union main Institutions

EU Parliament & Council of EU

- share legislative power (approve laws)

EU Commission

- **The executive body**; has the sole right to initiate proposals for new laws.

REGULATORY BODIES IN EU related to therapy

Directorate-General for Energy

2013/59 Basic Safety Standard Directive (BSSD) EURATOM

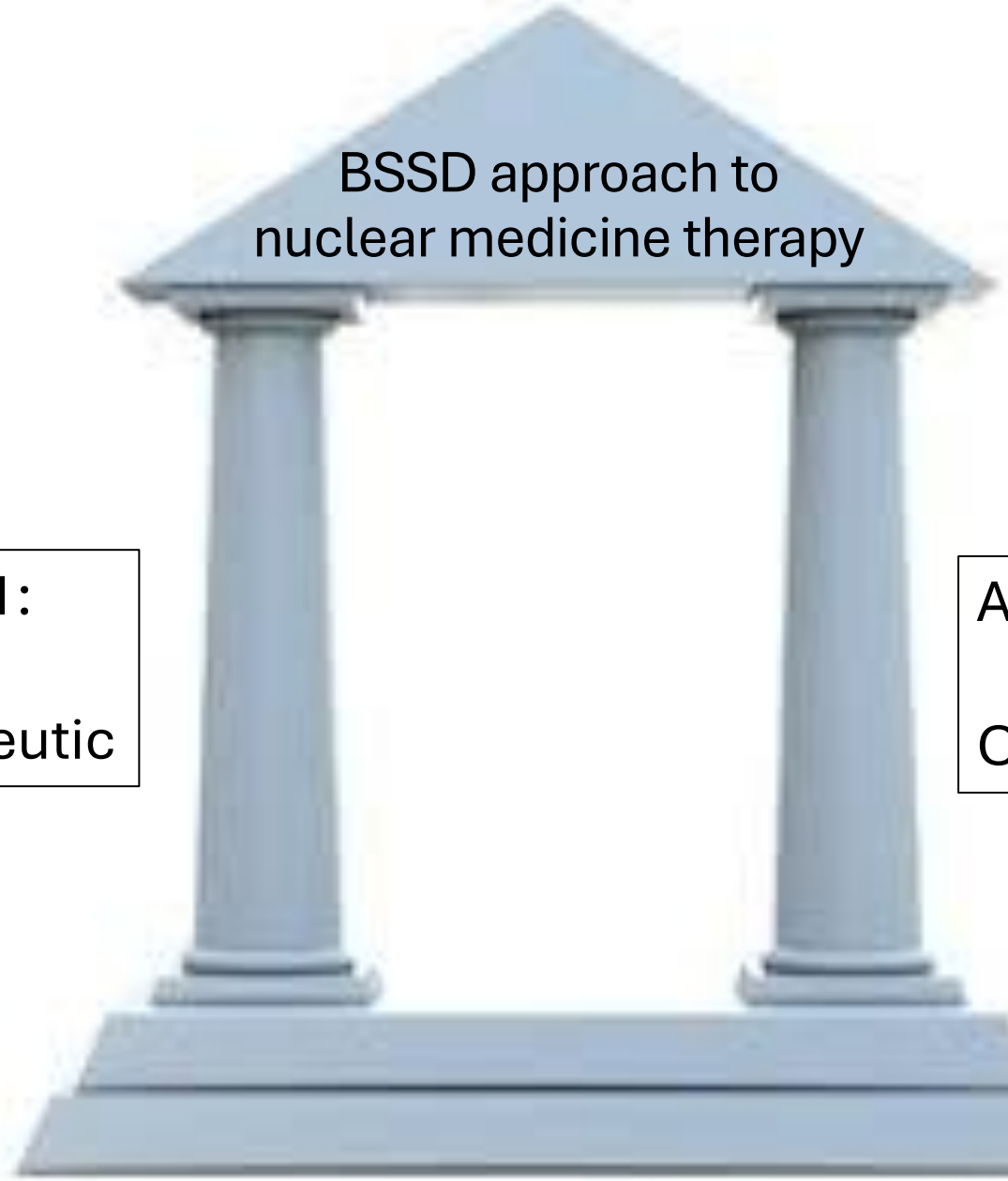
MEDICAL DEVICES (radiolabelled microspheres) are approved by Notified Bodies, which are designated and supervised by the national competent authorities of individual EU Member States

European Commission
Directorate-General for Health and Food Safety (DG SANTE)

2001/83 Directive: medicinal products for human use («Pharma Directive»)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Approval & Registration of Radio-pharmaceutical



Definition 81:

radiotherapeutic

Article 56:

Optimization

COUNCIL DIRECTIVE 2013/59/EURATOM

of 5 December 2013

laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom

Definition 81) "radioterapeutic":

means pertaining to radiotherapy,

including nuclear medicine for therapeutic purposes.

art 56: Optimization

...For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be **individually planned** and their delivery appropriately **verified** taking into account that **doses** to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.

Eur J Nucl Med Mol Imaging (2017) 44:1783–1786
DOI 10.1007/s00259-017-3707-3

EDITORIAL

The conflict between treatment optimization and registration of radiopharmaceuticals with fixed activity posology in oncological nuclear medicine therapy

C. Chiesa[1] · K. Sjogreen Gleisner[2] · G. Flux[3] · J. Gear[3] · S. Walrand[4] · K. Bacher[5] · U. Eberlein[6] · E. P. Visser[7] · N. Chouin[8] · M. Ljungberg[2] · M. Bardiès[9] · M. Lassmann[6] · L. Strigari[10] · M. W. Konijnenberg[11]

- Carlo Chiesa sent this editorial to the EMA Director Dr. Guido Rasi and to the Responsible of EMA onco pharma on 2 June 2017
- The appeal therein is not to force dosimetry to all centres, but to leave to possibility of optimization under the responsibility of each centre, without need of research approval
- No reply
- September 2017: EMA approved LUTATHERA with fixed posology
- EJNMMI (2023) Dieudonnè et al corrected our wrong statement that pharma regulation is in conflict with personalized administration

The “discovery” of the favourable legislation

EFOMP policy statement NO. 19: Dosimetry in nuclear medicine therapy – Molecular radiotherapy

Katarina Sjögreen-Gleisner[a,*,1], Glenn Flux[b,1], Klaus Bacher[c], Carlo Chiesa[d], Robin de Nijs[e], George C. Kagadis[f], Thiago Lima[g], Maria Lyra Georgosopoulou[h], Pablo Minguez Gabiña[i], Stephan Nekolla[j], Steffie Peters[k], Joao Santos[l], Bernhard Sattler[m], Caroline Stokke[n], Johannes Tran-Gia[o], Paddy Gilligan[p], Manuel Bardiès[q]

Physica Medica 2023

1. EU Directive 2013/59/EURATOM Basic Safety Standards (BSSD) for protection against the dangers arising from exposure to ionising radiation

2. Directive 2001/83/EC relating to medicinal products for human use

3. Regulation EU 2017/745 on medical devices

The Pharma Directive (going to be replaced)

https://eur-lex.europa.eu/eli/dir/2001/83/oj/eng

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

- (18)) Any rules governing **radiopharmaceuticals** must take into account the provisions of Council Directive 84/466/Euratom of 3 September 1984 **[at present replaced by the BSSD]…**

This item is preserved in the last draft of the new Pharma Directive

Note the attention paid by the Pharma Directive to radiation protection principles regarding radiopharmaceuticals administration.
The word “radiopharmaceutical/s appears 28 times.
Only 2 times in the BSSD.

The Pharma Directive

Article 4

1. Nothing in this Directive shall in any way derogate from the Community rules for the **radiation protection** of persons undergoing medical examination or **treatment**, or from the Community rules laying down the **basic safety standards** for the health protection of the general public and workers against the dangers of ionizing radiation.

This item was removed in the last draft of the new Pharma Directive

The Pharma directive

Attachment I, Part 3, Introduction

4. For **radiopharmaceuticals**, it is appreciated that toxicity may be associated with a **radiation dose**. [...] in therapy, it is the wanted property. The evaluation of safety and efficacy of radiopharmaceuticals shall, therefore, address requirements for medicinal products and **radiation dosimetry aspects**. **Organ/tissue exposure to radiation shall be documented**. **Absorbed radiation dose estimates shall be calculated** according to a specified, internationally recognized system by a particular route of administration.

This item is preserved in the last draft of the new Pharma Directive

Comment: The legal principle of the special law

Since 80ies, radioactive drugs (not yet defined radiopharmaceuticals) have been identified as a **special class** of medicines.

The *lex specialis* principle has to be applied.

Google AI: **lex specialis**,

The *lex specialis* principle, meaning "specific law overrides general law," is a legal maxim used to resolve conflicts between laws. It states that a more specific rule (**dosimetric optimization**) will take precedence over a more general one (**drug posology**) when both apply to the same situation, ensuring that specific provisions are not made meaningless.

Among many drugs,
we have……

Radio-pharmaceuticals. They are a special class of drugs. The principle of *the lex specialis* must be applied. This is the individual optimization.

Third directive to be considered:
MEDICAL DEVICES
(^{90}Y microspheres, ^{32}P particles)

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(Text with EEA relevance)

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745

Third directive to be considered:
MEDICAL DEVICES
(^{90}Y microspheres, ^{32}P particles)

(17) This Regulation should include requirements regarding the design and manufacture of devices emitting ionizing radiation without affecting the application of **Council Directive 2013/59/Euratom** which pursues other objectives.

16.4. Ionizing radiation

a) Devices intended to emit ionizing radiation shall be designed and manufactured taking into account the requirements of the **Directive 2013/59/Euratom** laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation

TAKE HOME MESSAGE

- **The Pharma and the Medical Device Directives refer to BSSD regarding radioactive therapeutic agents administration.**

- **The approval by EMA of therapeutic agents with fixed activity and number of administrations have no external legal support, except the registration EMA did.**

Legal analysis by a medical physicists and a lawyer

Stephan Walrand, Krystyna Bakhtina Phys Med (2022)

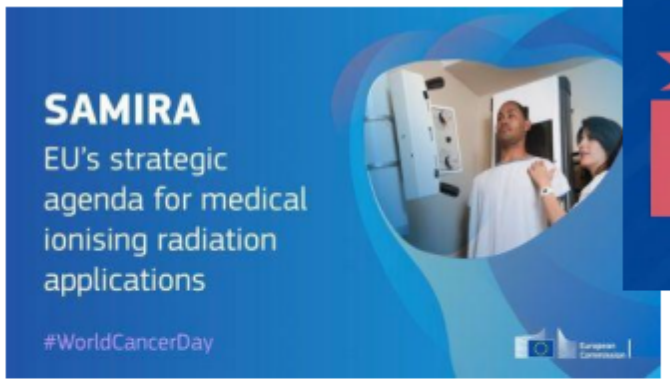
"…any power to adopt an EU measure that can alter an EU legislative act (like approving a radiopharmaceutical without optimization, n.d.r) *must be exercised by an EU institution that is democratically accountable, in other words by the Commission, which is ultimately accountable to the European Parliament.*

Such democratic oversight of the EMA still appears missing."

How could EMA approve therapeutic radiopharmaceuticals without possibility of optimization ?

To seek an answer to this hot question, EU Authorities undertook important actions, **for the first time in the history of nuclear medicine.**

SAMIRA Action Plan



FEB2021 The Commission adopted the

Strategic **A**genda for **M**edical **I**onising **R**adiation **A**pplications action plan

➠ To promote the **safe**, **high-quality**, and **reliable** use of **ionising radiation in healthcare**.

Supply of medical radioisotopes

Radiation quality and safety in medicine

Innovation and technological development

https://energy.ec.europa.eu/topics/nuclear-energy/radiological-and-nuclear-technology-health/samira-action-plan_en

Service Contract N°ENER/2022/NUCL/SI2.869532

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

- **Challenges due to a complex and fragmented regulatory framework regarding preparation and use of therapeutic radiopharmaceuticals**

  - **Pharma Directive**

  - **BSSD Directive**

- SAMIRA Action Plan: analyse and address these challenges to ensure high quality of care and safety to Europe's patients and foster further innovation in the field

Simplerad

Timespan: May 2022 – April 2024

- **EIBIR**

  Krause, Bernd – scientific coordinator, WP4 lead, WP5 co-lead
  Hierath, Monika – project manager, WP5 lead, WP4 co-lead

  EIBIR project office
  Peld, Nathan D

- **EFOMP**

  Bardiès, Manuel – WP1 lead, WP3 co-lead
  Peters, Steffie – WP2 co-lead
  Stokke, Caroline – WP4 co-lead (also EANM)

- **EANM Forschungs GmbH**

  Herrmann, Ken – WP2 co-lead
  Verburg, Frederik – WP3 lead
  Gear, Jonathan – WP2 lead
  Laßmann, Michael – WP1/3 co-lead
  Stokke, Caroline – WP4 co-lead
  Covens, Peter
  Decristoforo, Clemens
  Patt, Marianne
  Schulze, Rico – WP1 co-lead

  EANM project office
  Zieglmeier, Moritz
  De Martini, Amélie

§implerad specific objectives

With respect to therapeutic nuclear medicine

1. **Analyse the interrelations** between Pharma and BSSD Directive (WP1)
2. **Survey** on the implementation of the relevant European legal requirements (WP2)
3. **Recommend** actions to advance the **coherent** implementation of the European legal requirements (WP3)

4. Workshop (WP4) (Brusselles 13 December 2024)
5. Management, coordination, dissemination (WP5)

WP3 findings

10 items prioritized in the Brusselles stakeholder meeting

1. **Insufficient linkage between the Pharma Directive /EMA guidance and the BSSD**
2. **Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine**
3. Lack of resources for dosimetry
4. Differences regarding status of MPEs (e.g., training, requirements, level of experience, responsibilities) between member states
5. Heterogeneity of dose constraints & patient-release criteria among member states

WP3 findings

10 items prioritized in the Brusselles stakeholder meeting

6. Heterogeneity of management of radioactive waste across member states
7. Differing guidance from professional societies for clinical practice
8. **Differing regulatory procedures between member states for drug development & clinical trials**
9. Insufficient specialist knowledge concerning nuclear medicine within various stakeholders regarding EU pharmaceutical and medicine as well as BSSD-related regulations
10. Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance

Simplerad

Final report available at

https://op.europa.eu/s/z4YL

SAMIRA Joint Action ≠ SAMIRA action plan

Preparatory Joint Action

PrISMA

Preparatory activities for
Implementation of quality and
Safety of
Medical Ionizing radiation
Applications

Under the EU's SAMIRA action plan, the **PrISMA**project:

- PI Charlotte Rosenbaum, Dutch National Institute for Public Health and the Environment (RIVM)
- Start date project: May 1st, 2024 (18 months) End November 2025
- Consortium composed by **health and radiation protection authorities** and **scientific and professional institutions**

11 EU Member States + Norway

- Goals:
  - To identify and bring together the **relevant stakeholders** in the area of quality and safety in the medical use of ionising radiation
  - To **propose objectives, scope and activities** of the future SAMIRA Joint Action

https://www.rivm.nl/en/international-projects/samira-prisma

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SAMIRA JA: a forum to exchange good practices between Member States

In the fields of **radiation protection and health care**:

- many concepts, objectives and solutions are **common** to Member States
- but there are also **national adaptations** that make each country unique.

A network of organisations with similar interests will serve as a source of experience and inspiration to develop **necessary tools adaptable to circumstances** in each Member States.

30 countries with Competent Authority, with Affiliated Entities

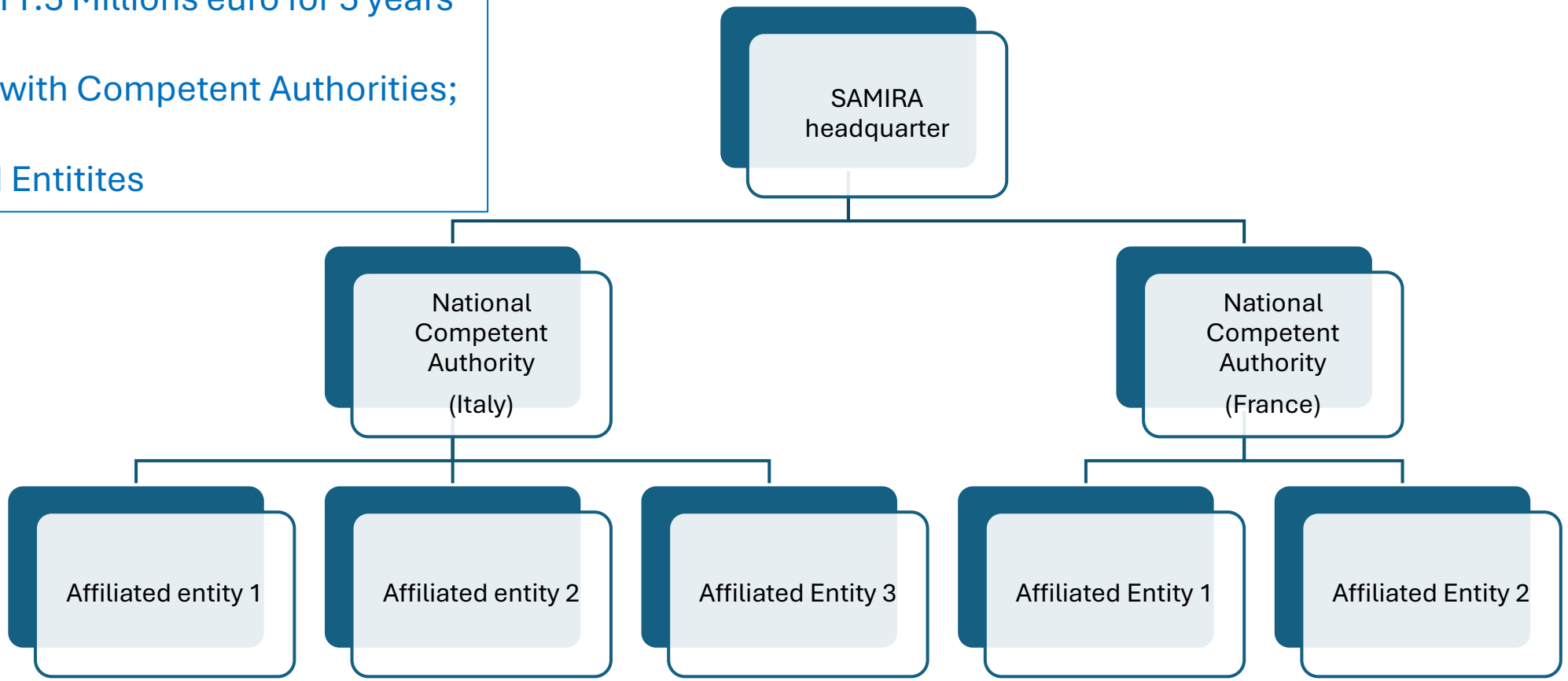
SAMIRA JOINT ACTION STRUCTURE

(Non-competitive participation)

EU Funding: 11.5 Millions euro for 5 years

30 countries with Competent Authorities;

246 Affiliated Entitites



SAMIRA JA - Mandatory Deliverables

- **Justification of diagnostic imaging**
  - Best practice guidance & procedures for **clinical audit of CT referrals**

- Procedures for **incident reporting** in radiotherapy and diagnostic/interventional radiology.

- Development/update of procedures for **patient dose recording & monitoring.**

[Senza titolo]

- Practical guidelines on **paediatric radiation protection optimisation**.

- Guidelines for **optimisation of image-guided radiotherapy (IGRT)**.

- Implementation of Council Directive (2013/59/Euratom) on optimisation & dosimetry **in radiopharmaceutical cancer therapy**.

In the meanwhile……..EMA is moving

For the first time in the history

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

07 October 2024
EMA/CHMP/451705/2024
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on clinical evaluation of therapeutic radiopharmaceuticals in Oncology

- EMA opened to suggestions by stakeholders regarding **the introduction of dosimetry in registration trials**
- Final aim: **creation of a workgroup to develop a guideline**

Key points to be addressed in the future guideline

- Standardisation of terminology
- exploration of a wide range of administered activity early in phase I/II trials to establish

  the maximum tolerated activity/**Absorbed Dose (AD)**,

  identify (acute) dose-limiting toxicities (DLTs),

  understand the relationship between administered activity and **AD**s,

  begin to gather data on dose-response for (late) radiation-induced toxicity.

- **Incorporation of systematic evaluation of dosimetry in the clinical development of tRPs**
- Specification of the data requirements allowing definition of posology for **individualized planning of the ADs in clinical routine**.

Key points to be addressed in the future guideline

- Guidance for management of acute toxicity in order to achieve short- and long-term **treatment optimization**, i.e., high likelihood of efficacy and tolerability with an acceptable risk of late toxicity.

- Guidance for specific tRPs/situations for which **challenges** are identified **in** performing direct **dosimetry analyses**.

- Development of strategies to achieve **optimisation of patient treatment** and **swift approval**.

- Discussion on the objectives of **individually optimised treatment** in late-stage versus curative setting

Next meeting (when ?)

On the other side of the Ocean……

FDA opened to suggestions by stakeholders regarding **the introduction of dosimetry in registration trials**

Oncology Therapeutic Radiopharmaceuticals: Dosage Optimization During Clinical Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comment collection closed on 20 October 2025

Introduction

- *This guidance is intended to assist sponsors in identifying an optimized dosage(s) (administered activity and schedule) for radiopharmaceutical therapies (RPTs) for oncology indications during clinical development and prior to submitting a marketing application*
- *dosage refers to **the** administered **activity** and schedule*
- *An optimized dosage is **the** administered activity and schedule that can maximize the benefit/risk profile or provide the desired therapeutic effect while minimizing toxicity*

- **No mention to** exposure, nor to **absorbed dose**, only activity considered
- No mention to **individual** optimization, only “the” optimal dosage for all patients
- Fixed activity choice once again. Nothing to do with EU BSSD 2013/59
- Concept without any legal support in EU, but impacting in EU, if a RP is produced and approved in USA !

Introduction

- *This guidance does not address **other aspects** of the clinical development of RPTs, for example use of dosimetry software, **use of fixed administered activity dosing for a population versus dosing determined by personalized dosimetry**, and theranostic co-development.*

A document focused on Dosage Optimization simply skips the issue of fixed activity versus personalized dosimetry.

The main issue for EMA of individualized therapy optimization is simply not addressed by FDA as “other aspects”

Background: **the search for MTD criticized**

- RPTs share characteristics with both cytotoxic chemotherapies and modern targeted oncology drugs

What a difference with definition 81) in the BSSD !

Thouh not explicitly here, everything is implicitily in terms of activity.

A. Participant population

- For participants treated previously with EBRT, eligibility for RPT trial enrollment should be determined by clinical variables such as pre-existing baseline toxicities and organ function.

Damage from previous irradiation could not manifest as baseline toxicity. Nevertheless the additional irradiation could impair organ function.

B. Trial design

- RPTs should generally be administered for a **fixed number of cycles** to mitigate the risk of delayed or cumulative toxicity. Protocols should pre-specify a **limit to the cumulative administered activity**, **and corresponding radiation absorbed doses to critical organs**, that is justified based on available data on RPT-specific organ tolerances.

Dosimetric optimization totally neglected

Reimbursement of dosimetry approved in Italy from 2025

Dosimetry is an ordinary clinical practice

92.19.A	TOMOSCINTIGRAFIA [SPET] SEGMENTARIA AI FINI DI PIANO DOSIMETRICO	€ 67,00
92.19.B	TOMOGRAFIA AD EMISSIONE DI POSITRONI [PET] SEGMENTARIA AI FINI DI PIANO DOSIMETRICO	€ 1.530,00

Only for out-patients: not for RLT, not for TARE

Reimbursement possible for iodine-131 out-patients.

Reimbursement only for the scan time, not for the calculation.

We asked to the Government wether the reimbursement for the calculation by Physicists acknowledged in EBRT could be used in nuclear medicine.

Conclusions

- **Fixed activity and fixed schedule are not supported by any EU directives**
- EU government and EMA started important actions to analyse the problem, for the first time in the history of nuclear medicine
- The FDA document is far from EU perspective, but it impacts on EU
- In Italy, scans for dosimetry are reimbursed as any ordinary clinical practice