Interrelations among Legal and Regulatory Frameworks

Session 2

14:15–15:15

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Results of analytical work and identified regulatory and implementation issues

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Presentation of WP1

WP1 Aims

- Analyse the interrelations between the authorisation regime for radiopharmaceuticals established under European pharmaceutical legislation and the dosimetry and related optimisation requirements established under the BSSD
- Analyse the applicable legal requirements as well as the relevant regulatory and authorisation instruments and practices established, with the view of identifying specific areas where their coherent implementation could be improved.
- Conduct a comparative analysis of the applicable regulatory frameworks in the EU, UK and USA

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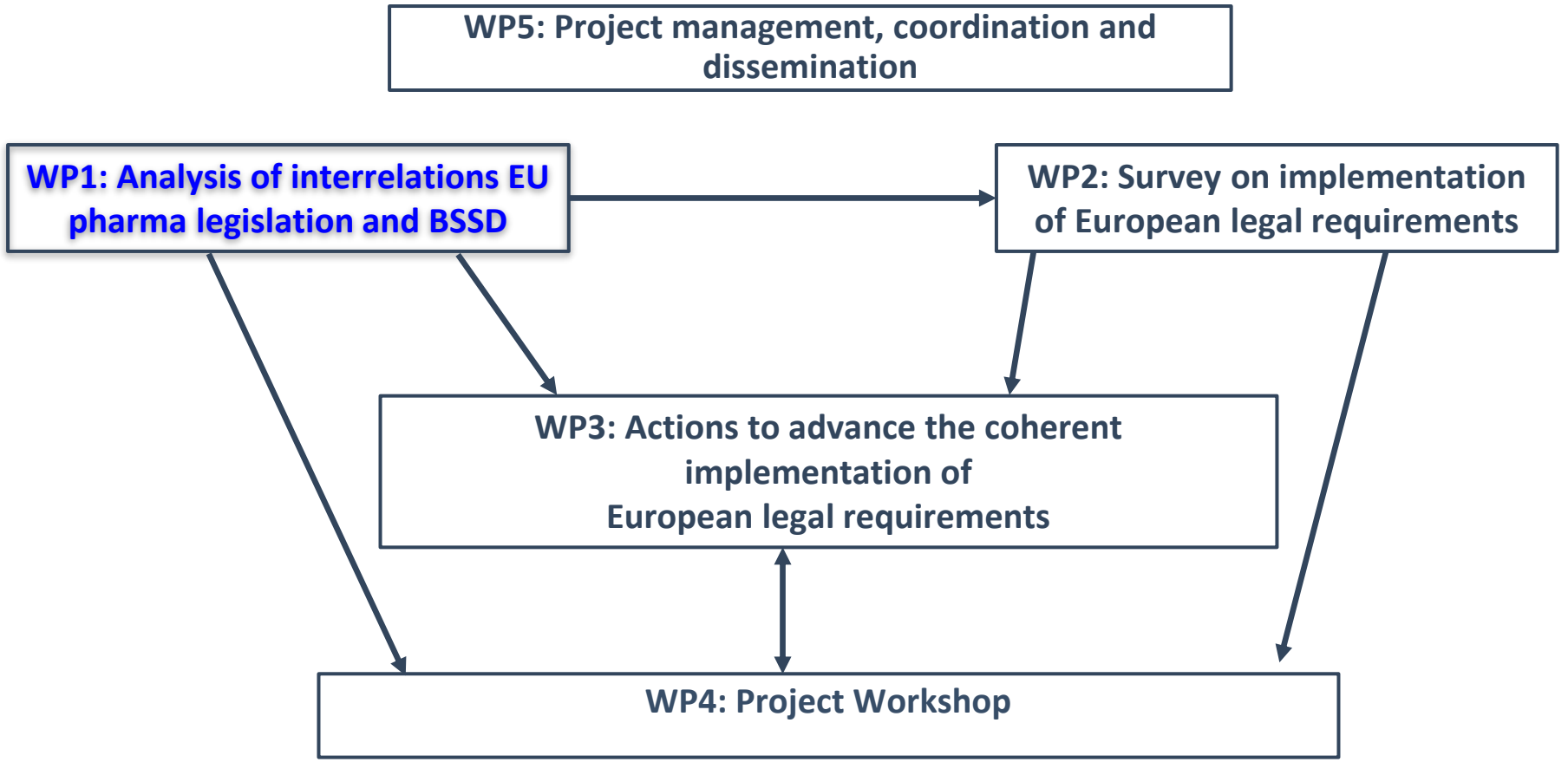
Work package structure and interrelations



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WP1 methodology

- Identification of relevant radiopharmaceuticals: 18 taken from EANM position paper
  - ^{177}Lu-labelled prostate-specific membrane antigen ligands were not initially considered, but since marketing authorisation for the US and UK in 2022, these regulatory situations were studied
  - Medical devices (^{90}Y microspheres) were added to the list after discussion
- Literature review: 129 references compiled and sorted in 7 major categories and ranked according to their importance
  - Regulatory documents, for EU, UK, US
  - Posologies
  - Medical devices
  - Position papers
  - Guidelines
  - International body global recommendations
  - Scientific references

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WP1 methodology

In-depth study of legal requirements in 7 countries: Finland, France, Germany, Italy, *Poland*, Spain & *Sweden*

1. What are the legal bodies in charge of the marketing authorisation of a therapeutic radiopharmaceutical in your country?
2. Are there institutions in charge of providing specific expertise in radiation safety and related fields to the regulatory authorities?
3. What are the interactions (if any) between the institutions in charge of giving the marketing authorisation (pharmaceutical) and those in charge of the implementation of the BSSD (radiation safety and optimisation)?
4. How is BSSD, and specifically article 56 on Optimisation, implemented in your country?
5. What is the situation in your country for the three following specific products: ^{131}I-NaI, ^{177}Lu-DOTATATE and ^{90}Y microspheres?

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WP1 findings

- Study of legal requirements in Finland, France, Germany, Italy, Poland, Spain, Sweden
  - The BSSD was transposed “faithfully” in all countries
  - All countries follow the marketing authorisation provided by the EMA (i.e., mostly fixed activities)
  - Countries are divided into those who acknowledge the existence of a problem between EMA and BSSD requirements, and those who do not:

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WP1 findings

- Germany, Italy and Sweden are trying to set up groups/write recommendations regarding the implementation of dosimetry in nuclear medicine therapy.
- France, Finland, Poland and Spain are either not mentioning an issue, or “give priority” to EMA (fixed activity)/EANM position statement (EMA-approved therapies are standard; therefore dosimetry is optional) and do not comply with the BSSD
- Since WP1 completion: situation is evolving in Spain, with a Royal Decree under review, proposing verification dosimetry to be implemented for therapeutic nuclear medicine, and planification and verification for clinical trials.

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WP1 findings

- Good practice examples for legal implementation for two commonly used therapeutic radiopharmaceuticals: (3 considered)
  - Radioiodine therapy of thyroid diseases (malignant and benign) with ^{131}I
  - Peptide receptor radionuclide therapy (PRRT) with [^{177}Lu]Lu-DOTATATE (Lutathera®)
  - Selective internal radiotherapy with ^{90}Y microspheres (SIR-Spheres®)

SmPC posolgies were checked against BSSD requirements

- ^{131}I-NaI and SIR-Spheres are not fully compliant
- Lutathera is not compliant (fixed activity approach)

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However, when looking at SmPC…

No reference to BSSD, optimisation, etc., but:

4.4 Special warnings and precautions for use

Individual benefit-risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effects

https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf
https://www.ema.europa.eu/en/documents/product-information/pluvicto-epar-product-information_en.pdf

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WP1 findings

- The lack of awareness among pharma regulators of the existence of article 56 of the BSSD is a major hurdle for its implementation
- The lack of intersection between EMA guidance documents and DG ENER directives on the specific subject of radioactive compounds for use in nuclear medicine therapy generates:
  - Confusion between the requirement for optimisation as stipulated in the BSSD and the need to follow the posology presented in the marketing authorisation
  - Lack of consideration in EMA guidance regarding marketing authorisations for items pertaining specifically to safety of radionuclides
  - Lack of European guidance for helping in implementing the BSSD

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WP1 findings

- The BSSD is a *lex specialis*
  - This means it has precedence over other directives
- Besides, in current "Pharma" Directive 2001/83/EC
  - *"Any rules governing radiopharmaceuticals must take into account the provisions of Council Directive 84/466/Euratom of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment".*

    Recital (18)
  - *"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".*

    Article 4, (1)

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Not often mentioned/known…

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WP1 findings

Since the end of WP1, four relevant documents were proposed:

- Proposal for a Directive of the European Parliament and of the Council on the Union Code Relating to Medicinal Products for Human Use, and Repealing Directive 2001/83/EC and Directive 2009/35/EC (new “Pharma” Directive)
  - (A first proposal was published in April 2023)
- EFOMP Policy Statement 19: Dosimetry in Nuclear Medicine Therapy – Molecular Radiotherapy
  - (Sjögreen-Gleisner et al. Phys Med https://doi.org/10.1016/j.ejmp.2023.103166)
- EANM Enabling Guide: How to Improve the Accessibility of Clinical Dosimetry
  - (Gear et al. EJNMMI. 2023;50:1861–1868)
- EANM Guidance Document: Dosimetry for First-in-Human Studies and Early Phase Clinical Trials
  - (Submitted to EJNMMI)

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Pharma Directive (proposal, may be removed)

- *"This Directive should be without prejudice to the provisions of Council Directive 2013/59/Euratom, including with respect to justification and optimisation of protection of patients and other individuals subject to medical exposure to ionising radiation. In the case of radiopharmaceuticals used for therapy, marketing authorisations, posology and administration rules have to notably respect that Directive's requirements that exposures of target volumes are to be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues are to be as low as reasonably achievable and consistent with the intended therapeutic purpose of the exposure"*

Recital (19)

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EFOMP PS 19

- EFOMP PS 19 summarises aspects of three directives relating to the therapeutic use of radiopharmaceuticals and medical devices, and outlines the steps needed for implementation of patient dosimetry for radioactive drugs
- To support the transition from administrations of fixed activities to personalised treatments based on patient-specific dosimetry, EFOMP presents a number of recommendations including:
  - Increased networking between centres and disciplines to support data collection
  - Development of codes-of-practice for harmonisation of dosimetry and patient outcome;
  - Resourcing to support an infrastructure that permits routine patient dosimetry;
  - Research funding to support investigation into individualised treatments;
  - Interdisciplinary training & education programmes
  - Support for investigator led clinical trials.

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EANM Enabling Guide

- This guide discusses the requirements for dosimetry and demonstrates how a dosimetry regimen can be tailored to the available facilities of a centre.
- The aim is to help centres wishing to initiate a dosimetry service but may not have the experience or resources of some of the established therapy and dosimetry centres.
- The multidisciplinary approach and different personnel requirements are discussed and key equipment reviewed with example protocols, demonstrating these factors are given in the supplementary material for the main therapies conducted in nuclear medicine, including:
  - ^{131}I NaI for benign thyroid disorders,
  - ^{177}Lu-DOTATATE and (^{131}I)-mIBG for neuroendocrine tumours,
  - ^{90}Y-microspheres for unresectable hepatic carcinoma.

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WP1 summary

- The BSSD specifically includes nuclear medicine therapy in the *radiotherapeutic* procedures
- BSSD has the precedence over other directives
- Current Pharma Directive acknowledges that fact; planned version may not
- SmPC also mention “some” possibility of irradiation optimisation requirement
  - This is now broadly known
  - Most (recent) radiopharmaceutical are administered without optimisation (planning and verify)

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