

Recommendations to Advance Coherent Implementation of European Legal Requirements

Session 4

09:10–10:50

Identification and prioritisation of issues

Erik Verburg

Presentation of WP3

WP3 Aims

- Identify and implement further actions to advance the coherent implementation of the European legal requirements with respect to therapeutic nuclear medicine, based on the issues identified by WP1 and WP2
- Address the issues presented in the introduction

Presentation of WP3

WP3 Methodology

- Review original list of issues to be addressed, based on outcome of literature review (WP1)
- Create combined list of itemised results from WP1 and WP2 and share with consortium and AB for ranking according to priority; 10 highest ranked priorities to be considered
- Draft proposal for action and remedies for the 10 priorities
- Stakeholder consultation
- Develop consensus guidance document

Presentation of WP3

WP3 grouping

- After review: initially 18 defined topics
- Considerable overlap between several issues
- After further consideration and analysis of WP2 data: 1 issue withdrawn
- Combining of items:
 - 5 items → Issue 1
 - 2 items → Issue 2
 - 2 items → Issue 3
 - 2 items → Issue 4

10 issues remaining → no further selection and prioritization necessary

1. Insufficient linkage between EU pharmaceutical legislation/EMA guidance & BSSD

| | Items from tender application | Items identified in WP1 | Items identified in WP2 |
|----|---|--|--|
| 1 | Lack of European guidance for implementing BSSD, pertaining to the specific difficulties faced in nuclear medicine beyond those encountered in X ray imaging or radiation therapy | The lack of intersection between EMA guidance documents and BSSD direct requirements on the specific subject of radioactive compounds for use in nuclear medicine therapy generates lack of European guidance for implementing the BSSD, pertaining to the specific difficulties faced by therapeutic nuclear medicine beyond those encountered in radiation therapy | |
| 2 | Lack of consideration in EMA guidance regarding marketing authorisations for items pertaining specifically to safety of radionuclides | The lack of intersection between EMA guidance documents and BSSD direct requirements on the specific subject of radioactive compounds for use in nuclear medicine therapy generates lack of consideration in EMA guidance regarding marketing authorisations for items pertaining specifically to safety of radionuclides | |
| 3 | Confusion between the requirement for optimisation stipulated in the BSSD and the need to follow the posology of the product used for marketing authorisation | The lack of intersection between EMA guidance documents and BSSD direct requirements 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 | On the question "In your country is it allowed to administer authorised therapeutic radionuclides outside of the posology indicated on the package insert?" We received a variation in responses from country to country and conflicting answers between correspondents and stakeholders from the same country |
| 12 | | Concerning biomedical research, since January 2022, all clinical studies with radiopharmaceuticals have to be handled centrally in CTIS. For CTIS, pertinent information regarding radiation protection in biomedical research is not being specifically taken into account at EU level. Furthermore, since time to complete reviews of applications on a national level within the new system is very short and no additional documentation can be requested from applicants, it will be very challenging (if not impossible) to estimate risk-benefit with regard to radiation exposure by the competent authority and may lead to rejection in cases of doubt | |
| 15 | | | Lack of understanding of article 56 of the 2013 Euratom directive within medicine authorities (national/EMA) as it is outside the current scope of medicines regulations; i.e., from a legal point of view it is not their responsibility to know |

2. Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine

| | Items from Itender application | Items identified in WP1 | Items identified in WP2 |
|----|---|--|--|
| 4 | Lack of clarity in the need for qualitative assessment of delivery verification or a requirement for quantitative analysis based on dosimetry indices | The BSSD specifically includes nuclear medicine therapy in the radiotherapeutic procedures, yet, even though the terms planification and verification are very well adopted in external beam radiotherapy, clarification is needed regarding the definition of an appropriate delivery verification: qualitative or quantitative (dosimetry-based) assessment? precision and associated methodology to comply with the individual planification of target volume exposures as required (“shall”) by the BSSD | <p>Interpretation of article 56 of the 2013 Euratom directive is unclear (i.e., multiple different strategies are thought to be able to satisfy these requirements as shown from a survey of the field) with regard to a. treatment planning and b. appropriate verification of delivery where it comes to radionuclide therapy. NOTE: majority of respondents construed A56 to indicate dosimetry, but regulations required differently.</p> <p>When asked what national regulations/ guidance recommends many stakeholders indicated optimisation was not recommended. Some stakeholders strongly thought optimisation was not relevant for nuclear medicine therapies</p> |
| 10 | Lack of clarity of the level of optimisation required to comply with European directives on, e.g., patient selection, imaging, dosimetry | | |

3. Lack of resources for dosimetry

| | Items from literature study in tender application | Items identified in WP1 | Items identified in WP2 |
|----|---|-------------------------|---|
| 5 | Lack of medical-physics expertise and physicians' knowledge of dosimetry in many nuclear medicine centres, stifling BSSD implementation | | Lack of knowledge and know-how of radionuclide therapy dosimetry (technologists, physicians, physicists etc.) |
| 17 | | | Shortage of funding for dosimetry |

4. Differences regarding status of MPEs between member states

| | Items from tender application | Items identified in WP1 | Items identified in WP2 |
|----|--|-------------------------|---|
| 6 | Divergent interpretation within the EU regarding the definition of standardised therapeutic procedures | | |
| 18 | | | Differences in definition and competencies of MPE between countries as well as legal requirements on the number of MPEs |

Withdrawn

| | Items from Itender application | Items identified in WP1 | Items identified in WP2 |
|---|---|-------------------------|---|
| 7 | Lack of data to make dosimetric comparison for treatment verification | | Scientific evidence was scored lowest by stakeholders in WP2 when asked what was limiting the implementation of planning and verification |

Presentation of WP3

WP3 — Outcome

- Consensus guidance document and recommendations
 - Draft document provided to Advisory Board in October
 - Consultation in November/December with workshop participants, HERCA WGMA, SGQS, EMA and Advisory Board
 - Workshop feedback to be integrated
 - Final version in a ready-to-publish format expected in April 2024 in the consortium's final report

Presentation of WP3

WP3 — 10 priorities to be addressed

1. Insufficient linkage between EU pharmaceutical legislation/EMA guidance and 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

Presentation of WP3

WP3 — 10 priorities to be addressed

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. Sufficient 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

1. Insufficient linkage between EU pharmaceutical legislation/EMA guidance & BSSD

Issues

- 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 pharmaceutical legislation/EMA guidance regarding marketing authorisations for items pertaining specifically to safety of radionuclides
- Lack of European guidance for implementing the BSSD, pertaining to the specificities of therapeutic nuclear medicine beyond those encountered in radiation therapy

2. Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine

Issues

- Lack of European guidance for implementing the BSSD
- Need for clarification on the level of precision & associated methodology to comply with the mandate of "individually planned exposures" as required by the BSSD

3. Lack of resources for dosimetry

Issues:

- Lack of resources in terms of **finance**, **know-how** and **sufficiently trained technical, medical and physics staff** in nuclear medicine centres
- Lack of **reimbursement for dosimetry**
- Lack of clinical operating procedures associated to guidelines

4. Differences regarding status of MPEs between member states

Issues

- Differences regarding status of MPEs (e.g., training, requirements, level of experience, responsibilities) between member states
- In WP2 80% of responders indicated that there was room for improvement regarding the role of MPEs

5. Heterogeneity of dose constraints & patient release criteria between member states

Issues

- Lack of harmonisation regarding patient release criteria & patient instructions among EU member states

6. Heterogeneity of management of radioactive waste across member states

Issues

- Management of radioactive waste is very effective in most countries across Europe
- However, huge heterogeneity of the specific conditions across member states and centres, hampering patient access to treatments
- Unclear radiological assessment used to establish these conditions

7. Differing guidance from professional societies for clinical practice

Issues

- For radionuclide therapy, different professional societies are coming to different, even contradictory, guidance for the same disease/therapeutic modality

8. Differing regulatory procedures between member states for drug development & clinical trials

Issues

- **Lack of sufficient knowledge** regarding radiation protection/pharmaceutical legislation & procedures in the respective national government bodies
- Differing regulatory processes between member states for drug development and clinical trials with radiopharmaceuticals
- **Lack of a combined approach to process pharmaceutical and radiation protection application documents for clinical studies with radiopharmaceuticals**

9. Lack of specialist knowledge regarding EU pharmaceutical and medicine as well as BSSD related regulations

Issues

- National regulators have different levels of knowledge in one or even both sets of legislation and their implementation for nuclear medicine practice

10. Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance

Issues

- Regulatory guidance differs between therapies, countries and at least for some therapies, and guidance might differ from professional opinion
- It is important that users understand the possibilities on treatment adaptation based on legislation while taking into account expert opinion

Conclusion

- The results of literature and legal texts reviewed for the Tender and WP1 as well as the results of the interviews and surveys were analyzed
- 10 issues were identified which required further actions to advance the coherent implementation of the European legal requirements with respect to therapeutic nuclear medicine
- Recommendations will be made and discussed (next speakers)